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NEWS 11	Jun 10	PCTFULL has been reloaded
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NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
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NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 26	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 27	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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FILE 'CAPLUS' ENTERED AT 13:15:21 ON 09 OCT 2002

=> s squalene
L1 13590 SQUALENE

=> s l1 and squalane
L2 512 L1 AND SQUALANE

=> s l2 and emulsion
L3 95 L2 AND EMULSION

=> s l3 and storage
L4 3 L3 AND STORAGE

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PROCESSING COMPLETED FOR L4
L5 3 DUP REMOVE L4 (0 DUPLICATES REMOVED)

=> d l5 1-3 cbib abs

L5 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS
2002:169523 Document No. 136:236673 **Emulsion** compositions containing retinyl palmitate for skin application. Hayase, Motoshi (Kanebo, Ltd., Japan). Jpn. Kokai Tokkyo Koho JP 2002068957 A2 20020308, 10 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 2001-170654 20010606. PRIORITY: JP 2000-176400 20000613.

AB The invention relates to an **emulsion** compn. for skin application contg. retinyl palmitate, wherein the stability of retinyl palmitate in the compn is improved by adding sorbitan monoisostearate and N-acylglutamate in the compn. A cream contg. sorbitan monoisostearate 0.5, stearic acid 1, behenyl alc. 2, self-emulsified glycerin monostearate 1.5, liq. paraffin 8, **squalene** 9, Bu paraben 0.1, sodium N-stearoyl-L-glutamate 1, Me paraben 0.2, dipotassium glycyrrhizinate 0.1, conc glycerin 0.1, dipropylene glycol 6, retinyl palmitate 0.1, and water q.s. to 100 % was formulated, and tested for its **storage** stability.

L5 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS
2001:472459 Document No. 135:66189 A stable immunogenic composition for frozen **storage** containing protein carriers. Grimes, Stephen; Blackburn, Peter (Aphton Corporation, USA). PCT Int. Appl. WO 2001045670 A2 20010628, 48 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US35248 20001222. PRIORITY: US 1999-PV173022 19991223.

AB An injectable vaccine compn. comprising an immunogenic conjugate in an **emulsion** contg. advantageous oily vehicles is disclosed as suitable for frozen **storage**; moreover, a water-in-oil **emulsion** compn. is found to enhance immunogenicity after **storage** at about -18.degree.. For example, an aq. phase droplets of an anti-gastrin immunogenic **emulsion** (e.g., human gastrin 17(1-9)Ser 9-diphtheria toxoid conjugate) were stable at -70.degree., -18.degree., and 4.degree., but less stable at 25.degree.. The conjugate purity was most stable at -70.degree. and -18.degree., less stable at 4.degree. and much less stable at 25.degree.. The behavior in the release assay was not altered by **storage** at any four select temps. The immunogenicity response was unaffected by **storage** at 4.degree.. **Storage** at -18.degree. increased immunogenicity. The finding that it was possible to enhance immunogenicity by a single freeze-thaw cycle (freezing at -18.degree.) was unexpected. Although **storage** at -70.degree. and 25.degree. resulted in more variable responses, there was no clear trend that might be predictive for length of feasible **storage** time; in addn., immunogenicity was not altered from the time 0 control. However, not all **emulsion** formulations showed the stable storability according to this invention. Accordingly, the **emulsions** capable of withstanding freezing have been found to include Montanide ISA 25, 703, 719, and 720.

L5 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2002 ACS
2000:889385 Document No. 134:46649 **Storage**-stable solid water-in-oil **emulsion** cosmetics containing polyoxyalkylene-polysiloxanes. Inagawa, Takashi; Nakayama, Junko; Itsumi, Takeshi (Kosei Co., Ltd., Japan). Jpn. Kokai Tokkyo Koho JP 2000351712 A2 20001219, 9 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1999-160175 19990607.

AB The cosmetics contain long-chain polyoxyalkylene-polysiloxanes (A), oily solids (B) having m.p. .ltoreq.80.degree., oils and/or oily pastes (C) contg. volatile silicone oils, and 55-90 wt.% aq. components (D) at the wt. ratios of (A + B + C):B of 5:1 to 20:1. A cosmetic cream contg. Abil EM 90 (long-chain polyoxyalkylene-polysiloxane) 1.0, decamethylcyclopentasiloxane 5.0, **squalane** 7.0, cetyl isooctanoate 5.0, candelilla wax (m.p. 70.degree.) 2.0, tocopheryl acetate 0.2, perfume 0.1, Me p-hydroxybenzoate 0.1, 1,3-butylene glycol 15.0, Na citrate 1.0, and H2O 63.6 wt.% was stable at 5 or 40.degree. for 1 mo and gave sherbet-like refreshing feeling when applied to the skin.

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CAN --------- List of CA abstract numbers without answer numbers
CBIB -------- AN, plus Compressed Bibliographic Data
DALL -------- ALL, delimited (end of each field identified)
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FAM --------- AN, PI and PRAI in table, plus Patent Family data
FBIB -------- AN, BIB, plus Patent FAM
IND --------- Indexing data
IPC --------- International Patent Classifications
MAX --------- ALL, plus Patent FAM, RE
PATS -------- PI, SO
SAM --------- CC, SX, TI, ST, IT
SCAN -------- CC, SX, TI, ST, IT (random display, no answer numbers;
SCAN must be entered on the same line as the DISPLAY,
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STD --------- BIB, IPC, and NCL

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IALL -------- ALL, indented with text labels
IBIB -------- BIB, indented with text labels
IMAX -------- MAX, indented with text labels
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OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
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containing hit terms
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HITSTR ------ HIT RN, its text modification, its CA index name, and
its structure diagram
HITSEQ ------ HIT RN, its text modification, its CA index name, its
structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and
its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its
structure diagram, plus NTE and SEQ fields
KWIC -------- Hit term plus 20 words on either side
OCC --------- Number of occurrence of hit term and field in which it occurs

To display a particular field or fields, enter the display field codes. For a list of the display field codes, enter HELP DFIELDS at an arrow prompt (=>). Examples of formats include: TI; TI,AU; BIB,ST; TI,IND; TI,SO. You may specify the format fields in any order and the information will be displayed in the same order as the format specification.

All of the formats (except for SAM, SCAN, HIT, HITIND, HITRN, HITSTR, FHITSTR, HITSEQ, FHITSEQ, KWIC, and OCC) may be used with DISPLAY ACC to view a specified Accession Number.
ENTER DISPLAY FORMAT (BIB):bib

L5 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS
AN 2002:169523 CAPLUS
DN 136:236673
TI **Emulsion** compositions containing retinyl palmitate for skin application
IN Hayase, Motoshi
PA Kanebo, Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 10 pp.

CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 2002068957	A2	20020308	JP 2001-170654	20010606
PRAI	JP 2000-176400	A	20000613		

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 13:15:21 ON 09 OCT 2002

L1 13590 S SQUALENE
L2 512 S L1 AND SQUALANE
L3 95 S L2 AND EMULSION
L4 3 S L3 AND STORAGE
L5 3 DUP REMOVE L4 (0 DUPLICATES REMOVED)

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L6 23 L3 AND COMPOSITION

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L7 2 L6 AND IMMUNOGENIC

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L8 2 DUP REMOVE L7 (0 DUPLICATES REMOVED)

=> d l8 1-2 cbib abs

L8 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
2001:472459 Document No. 135:66189 A stable **immunogenic composition** for frozen storage containing protein carriers. Grimes, Stephen; Blackburn, Peter (Aphton Corporation, USA). PCT Int. Appl. WO 2001045670 A2 20010628, 48 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US35248 20001222. PRIORITY: US 1999-PV173022 19991223.

AB An injectable vaccine **compn.** comprising an **immunogenic** conjugate in an **emulsion** contg. advantageous oily vehicles is disclosed as suitable for frozen storage; moreover, a water-in-oil **emulsion compn.** is found to enhance immunogenicity after storage at about -18.degree.. For example, an aq. phase droplets of an anti-gastrin **immunogenic emulsion** (e.g., human gastrin 17(1-9)Ser 9-diphtheria toxoid conjugate) were stable at -70.degree., -18.degree., and 4.degree., but less stable at 25.degree.. The conjugate purity was most stable at -70.degree. and -18.degree., less stable at 4.degree. and much less stable at 25.degree.. The behavior in the release assay was not altered by storage at any four select temps. The immunogenicity response was unaffected by storage at 4.degree.. Storage at -18.degree. increased immunogenicity. The finding that it was possible to enhance immunogenicity by a single freeze-thaw cycle (freezing at -18.degree.) was unexpected. Although storage at -70.degree. and

25.degree. resulted in more variable responses, there was no clear trend that might be predictive for length of feasible storage time; in addn., immunogenicity was not altered from the time 0 control. However, not all **emulsion** formulations showed the stable storability according to this invention. Accordingly, the **emulsions** capable of withstanding freezing have been found to include Montanide ISA 25, 703, 719, and 720.

L8 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
2001:100935 Document No. 134:161876 Fusion proteins of B- and T-cell epitopes of the HER-2 protein for use in cancer vaccines. Kaumaya, Pravin T.; Stevens, Vernon C.; Triozzi, Pierre L. (The Ohio State University, USA). PCT Int. Appl. WO 2001008636 A2 20010208, 51 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US21222 20000803. PRIORITY: US 1999-PV146869 19990803.
AB **Compns.** for stimulating the immune system and for treating malignancies assocd. with overexpression of the HER-2 protein are provided. Such **compns.** include **immunogenic** epitopes of the HER-2 proteins and chimeric and multivalent peptides which comprise such epitopes. The present invention also relates to polynucleotides which encode the chimeric peptides. Also provided are pharmaceutical **compns.** comprising such **immunogenic compns.** Methods for stimulating an immune response to HER-2 protein are provided. Methods for treating breast cancer, ovarian cancer, prostate cancer, colon cancer and lung cancer are provided. Mice immunized with these peptides mounted a very strong immune response with antibody titers for some peptides reaching >250,000 with IgG1 and IgG2 as the major isotype.

=> s montanide ISA 703
L9 2 MONTANIDE ISA 703

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PROCESSING COMPLETED FOR L9
L10 2 DUP REMOVE L9 (0 DUPLICATES REMOVED)

=> d l10 1-2 cbib abs

L10 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
2001:472459 Document No. 135:66189 A stable immunogenic composition for frozen storage containing protein carriers. Grimes, Stephen; Blackburn, Peter (Aphton Corporation, USA). PCT Int. Appl. WO 2001045670 A2 20010628, 48 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US35248 20001222. PRIORITY: US 1999-PV173022 19991223.
AB An injectable vaccine compn. comprising an immunogenic conjugate in an emulsion contg. advantageous oily vehicles is disclosed as suitable for frozen storage; moreover, a water-in-oil emulsion compn. is found to enhance immunogenicity after storage at about -18.degree.. For example, an aq. phase droplets of an anti-gastrin immunogenic emulsion (e.g., human gastrin 17(1-9)Ser 9-diphtheria toxoid conjugate) were stable at -70.degree., -18.degree., and 4.degree., but less stable at 25.degree.. The conjugate purity was most stable at -70.degree. and -18.degree., less stable at 4.degree. and much less stable at 25.degree.. The behavior in the release assay was not altered by storage at any four select temps. The immunogenicity response was unaffected by storage at 4.degree..

Storage at -18.degree. increased immunogenicity. The finding that it was possible to enhance immunogenicity by a single freeze-thaw cycle (freezing at -18.degree.) was unexpected. Although storage at -70.degree. and 25.degree. resulted in more variable responses, there was no clear trend that might be predictive for length of feasible storage time; in addn., immunogenicity was not altered from the time 0 control. However, not all emulsion formulations showed the stable storability according to this invention. Accordingly, the emulsions capable of withstanding freezing have been found to include Montanide ISA 25, 703, 719, and 720.

L10 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
2001:359834 Document No. 134:365700 Improved method of immunization by separate administration of immunogen and immunostimulant. Gevas, Philip C.; Michaeli, Dov; Grimes, Stephen (Aphton Corporation, USA). PCT Int. Appl. WO 2001034192 A2 20010517, 20 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US30778 20001108. PRIORITY: US 1999-PV164054 19991108.
AB A method for improving the immune response to a immunogen by sep. administering to a patient an immunogen compn. for sustained release comprising an epitope of the immunogen target, and a supplement comprising an adjuvant compd. for stimulating, potentiating or activating a strong immune response. The provided method potentially reduces local irritation at the sites of inoculation, i.m. or s.c.

=> s Monanide ISA 25
L11 0 MONANIDE ISA 25

=> s montanide ISA 25 or ISA 703 or ISA 719 or ISA 720
L12 78 MONTANIDE ISA 25 OR ISA 703 OR ISA 719 OR ISA 720

=> dup remove l12
PROCESSING COMPLETED FOR L12
L13 42 DUP REMOVE L12 (36 DUPLICATES REMOVED)

=> s l13 and vaccine
L14 36 L13 AND VACCINE

=> dup remove l14
PROCESSING COMPLETED FOR L14
L15 36 DUP REMOVE L14 (0 DUPLICATES REMOVED)

=> d l15 1-36 cbib abs

L15 ANSWER 1 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2002144102 EMBASE Stratified and cryogenically stored (SACS) **vaccines**, a new concept in emergency foot-and-mouth disease **vaccine** formulation and storage. Barnett P.V.; Statham R.J.. P.V. Barnett, Pirbright Laboratory, Institute for Animal Health, Ash Road, Pirbright, Woking, Surrey GU24 0NF, United Kingdom. paul.barnett@bbsrc.ac.uk. Vaccine 20/16 (2060-2064) 15 May 2002.
Refs: 11.
ISSN: 0264-410X. CODEN: VACCDE.
Publisher Ident.: S 0264-410X(02)00052-X. Pub. Country: United Kingdom.
Language: English. Summary Language: English.
AB Strategic reserves of foot-and-mouth disease (FMD) antigen have become an

integral part of FMD control policy for many countries. They are based on two principles, ready formulated **vaccine** stored at +4.degree.C, or concentrated antigen preparations held at ultra-low temperature for later formulation. However, the latter is more economical, since ready formulated **vaccine**, based on oil or aluminium hydroxide/saponin adjuvants, requires regular replacement. This is primarily the result of the **vaccine**'s limited shelf-life, nominally 18 months at +4.degree.C. Unfortunately, lowering the temperature of storage, in a bid to extend its shelf-life, has a detrimental effect on the **vaccine** 's potency. Montanide ISA 206 and 25, two 'ready-to-formulate' oil adjuvants which can be used in all target species, are ideal for emergency vaccination. Their potential is enhanced by the ease in which they are formulated into oil emulsion **vaccines**. Here we describe a novel approach of layering the individual components of FMD **vaccine** in the same primary container and then storing the product at ultra-low temperature. This avoids the detrimental effect on potency, normally observed with frozen formulated FMD **vaccine**, and could substantially extend the products shelf-life. The implications of this approach for emergency vaccination strategy are discussed.

L15 ANSWER 2 OF 36 EMBASE
2002175103 EMBASE Adjuvants and malaria **vaccine** development. Xiao L.; Rafi-Janajreh A.; Patterson P.; Zhou Z.; Lal A.A.. A.A. Lal, Ctr. for Disease Control/Prevention, Mail-stop: F-12, 4770 Buford Highway, Chamblee, GA 30341, United States. ALal@cdc.gov. Chemical Immunology 80/- (343-365) 2002.
Refs: 104.
ISSN: 1015-0145. CODEN: CHMIEP. Pub. Country: Switzerland. Language: English.

L15 ANSWER 3 OF 36 CAPLUS
2002:510636 Montanide **ISA 720** and 51: a new generation of water in oil emulsions as adjuvants for human **vaccines**. Aucouturier, Jerome; Dupuis, L.; Deville, S.; Ascarateil, S.; Ganne, V. (SEPPIC, Paris, 75321, Fr.). Expert Review of Vaccines, 1(1), 111-118 (English) 2002. CODEN: ERVXAX. ISSN: 1476-0584. Publisher: Future Drugs Ltd..
AB The development of adjuvants will represent a major challenge for this century. Indeed the need for safer **vaccines** leads to the development of a new generation of antigens like synthetic peptide, recombinant proteins or even vectored DNA. However, this is to the detriment of their immunogenicity. The addn. of adjuvant is becomes necessary to enhance immune responses and improve **vaccine** potency. However, adjuvants can be responsible for the apparition of secondary reactions and they must be adapted according to various criteria such as the route of immunization, the type of the immune response, the duration of immunity, or the quality of the antigen, in order to get the best balance between efficacy and safety.

L15 ANSWER 4 OF 36 CAPLUS
2001:713379 Document No. 135:271884 Molecule of pharmaceutical interest comprising at its N-terminal a glutamic acid or a glutamine in the form of a physiologically acceptable strong acid. Klinguer-Hamour, Christine; Corvaia, Nathalie; Beck, Alain; Goetsch, Liliane (Pierre Fabre Medicament, Fr.). PCT Int. Appl. WO 2001070772 A2 20010927, 149 pp. DESIGNATED STATES: W: AU, BR, CA, CN, JP, MX, US, ZA; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (French). CODEN: PIXXD2. APPLICATION: WO 2001-FR872 20010322. PRIORITY: FR 2000-3711 20000323.
AB The invention concerns a mol. of pharmaceutical interest, preferably a major histocompatibility complex (MHC) ligand, comprising a glutamic acid or a glutamine at its N-terminal, in the form of a physiol. acceptable

addn. salt, and a **vaccine** comprising such a ligand. The **vaccines** may be used against tumors, bacteria, viruses, parasites, etc.

L15 ANSWER 5 OF 36 CAPLUS COPYRIGHT 2002 ACS
2001:472459 Document No. 135:66189 A stable immunogenic composition for frozen storage containing protein carriers. Grimes, Stephen; Blackburn, Peter (Aphton Corporation, USA). PCT Int. Appl. WO 2001045670 A2 20010628, 48 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US35248 20001222. PRIORITY: US 1999-PV173022 19991223.
AB An injectable **vaccine** compn. comprising an immunogenic conjugate in an emulsion contg. advantageous oily vehicles is disclosed as suitable for frozen storage; moreover, a water-in-oil emulsion compn. is found to enhance immunogenicity after storage at about -18.degree.. For example, an aq. phase droplets of an anti-gastrin immunogenic emulsion (e.g., human gastrin 17(1-9)Ser 9-diphtheria toxoid conjugate) were stable at -70.degree., -18.degree., and 4.degree., but less stable at 25.degree.. The conjugate purity was most stable at -70.degree. and -18.degree., less stable at 4.degree. and much less stable at 25.degree.. The behavior in the release assay was not altered by storage at any four select temps. The immunogenicity response was unaffected by storage at 4.degree.. Storage at -18.degree. increased immunogenicity. The finding that it was possible to enhance immunogenicity by a single freeze-thaw cycle (freezing at -18.degree.) was unexpected. Although storage at -70.degree. and 25.degree. resulted in more variable responses, there was no clear trend that might be predictive for length of feasible storage time; in addn., immunogenicity was not altered from the time 0 control. However, not all emulsion formulations showed the stable storability according to this invention. Accordingly, the emulsions capable of withstanding freezing have been found to include **Montanide ISA 25**, 703, 719, and 720.

L15 ANSWER 6 OF 36 CAPLUS COPYRIGHT 2002 ACS
2001:359834 Document No. 134:365700 Improved method of immunization by separate administration of immunogen and immunostimulant. Gevas, Philip C.; Michaeli, Dov; Grimes, Stephen (Aphton Corporation, USA). PCT Int. Appl. WO 2001034192 A2 20010517, 20 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US30778 20001108. PRIORITY: US 1999-PV164054 19991108.
AB A method for improving the immune response to a immunogen by sep. administering to a patient an immunogen compn. for sustained release comprising an epitope of the immunogen target, and a supplement comprising an adjuvant compd. for stimulating, potentiating or activating a strong immune response. The provided method potentially reduces local irritation at the sites of inoculation, i.m. or s.c.

L15 ANSWER 7 OF 36 CAPLUS COPYRIGHT 2002 ACS
2001:265455 Document No. 134:309686 Compositions and methods for WT1 specific immunotherapy. Skeiky, Yasir A. W.; Xu, Jiangchun; Cheever,

Martin A.; Reed, Steven G. (Corixa Corporation, USA). PCT Int. Appl. WO 2001025273 A2 20010412, 228 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US27465 20001004. PRIORITY: US 1999-PV157459 19991004.

AB Compns. and methods for the therapy of malignant diseases, such as leukemia and cancer, are disclosed. The compns. comprise one or more of a WT1 polynucleotide, a WT1 polypeptide, an antigen-presenting cell presenting a WT1 polypeptide, an antibody that specifically binds to a WT1 polypeptide; or a T cell that specifically reacts with a WT1 polypeptide. Such compns. may be used, for example, for the prevention and treatment of metastatic diseases.

L15 ANSWER 8 OF 36 CAPLUS COPYRIGHT 2002 ACS

2001:851786 Document No. 136:4707 Immunostimulatory nucleic acids for inducing a Th2 immune response. McCluskie, Michael J.; Davis, Heather L. (Can.). U.S. Pat. Appl. Publ. US 2001044416 A1 20011122, 50 pp. (English). CODEN: USXXCO. APPLICATION: US 2001-768012 20010122. PRIORITY: US 2000-PV177461 20000120.

AB The invention relates to methods and products for inducing an immune response using immunostimulatory nucleic acids. In particular the immunostimulatory nucleic acids preferentially induce a Th2 immune response. The invention is useful for treating and preventing disorders assocd. with a Th1 immune response or for creating a Th2 environment for treating disorders that are sensitive to Th2 immune responses. These disorders include Th1-mediated disease, autoimmune disease, infection, and cancer.

L15 ANSWER 9 OF 36 MEDLINE

2001406639 Document Number: 21351514. PubMed ID: 11457560. A phase I clinical trial of a multi-epitope polypeptide TAB9 combined with Montanide **ISA 720** adjuvant in non-HIV-1 infected human volunteers.
Toledo H; Baly A; Castro O; Resik S; Laferte J; Rolo F; Navea L; Lobaina L; Cruz O; Miguez J; Serrano T; Sierra B; Perez L; Ricardo M E; Dubed M; Lubian A L; Blanco M; Millan J C; Ortega A; Iglesias E; Penton E; Martin Z; Perez J; Diaz M; Duarte C A. (Instituto de Medicina Tropical Pedro Kouri, Autopista Novia del Mediodia. Km 6, La Lisa. Apdo 601, Marianao 13, 11300, Ciudad Habana, Cuba.) VACCINE, (2001 Jul 20) 19 (30) 4328-36. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB A phase I clinical trial was performed to examine the safety and immunogenicity of a multi-epitope polypeptide comprising the central 15 amino acids of the V3 loop from six HIV-1 isolates. This protein called TAB9 was emulsified in Montanide ISA720 (Seppic, Paris) and administered intramuscularly at doses of 0, 0.2 and 1 mg to 24 healthy, HIV-1 seronegative adult males. Three immunisations were given at months 0, 1 and 6 in a randomised, double blind, placebo controlled clinical trial. The placebo was generally well tolerated. However, severe local reactions were observed in TAB9 vaccinated subjects after the second and third inoculations. Seven out of eight volunteers from the lower dose group showed moderate or severe local inflammation, while four out of eight subjects from the higher dose group developed granulomas and sterile abscesses. In general, the reactogenicity depended on the number of inoculations given and the dose of TAB9. Both doses were immunogenic, all immunised volunteers seroconverted and antibodies were broadly reactive against the V3 peptides included in the protein. All **vaccine**'s sera reacted against gp120 in Western blot and 50% of them also

neutralised at least one out of five laboratory isolates tested. No differences between doses were found. Anti TAB9 lymphoproliferative responses were observed, being more intense in the high dose group. Due to the strong local reactions that were found in this study, a change in the formulation will be required for further trials with this **vaccine** candidate in humans.

L15 ANSWER 10 OF 36 SCISEARCH COPYRIGHT 2002 ISI (R)
2001:615396 The Genuine Article (R) Number: 456NZ. Induction of a cytotoxic T-cell response to HIV-1 proteins with short synthetic peptides and human compatible adjuvants. Peter K (Reprint); Men Y; Pantaleo G; Gander B; Corradin G. Univ Lausanne, Inst Biochem, Chemin Boveresses 155, CH-1066 Epalinges, Switzerland (Reprint); Univ Lausanne, Inst Biochem, CH-1066 Epalinges, Switzerland; ETH Zurich, Inst Pharmaceut Sci, Zurich, Switzerland; CHU Vaudois, Div Infect Dis, CH-1011 Lausanne, Switzerland. VACCINE (20 JUL 2001) Vol. 19, No. 30, pp. 4121-4129. Publisher: ELSEVIER SCI LTD. THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND. ISSN: 0264-410X. Pub. country: Switzerland. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB The goal of this study was the induction of a strong CTL response against multiple CTL epitopes present in HIV proteins using short synthetic peptides. Four HLA-A2.1 restricted peptides (RT 476-484, p17 77-85, gp41 814-823, RT 956-964) that showed stable binding to the HLA-A2.1 molecule in an in vitro binding assay were able to elicit a strong specific immune response in HLA-A2.1 transgenic mice when injected with IFA or Montanide((R)). The use of biodegradable microspheres (MS) as adjuvant was also successfully tested for all peptides. When the peptides were injected as a mixture the response was weaker as compared to individual injections of the peptides indicating the occurrence of immunodominance (ID). We are currently investigating whether ID can be overcome by a combined injection of peptide loaded MS with different release patterns. Taken together, it seems feasible to induce a specific CTL response in HLA-A2.1 transgenic mice against several HIV proteins using short synthetic peptides and human compatible adjuvants. (C) 2001 Elsevier Science Ltd. All rights reserved.

L15 ANSWER 11 OF 36 CAPLUS COPYRIGHT 2002 ACS
2002:472276 Lipopeptide **vaccines**: a strategy for improving protective immunity against influenza. Deliyannis, Georgia; Jackson, David C.; Harling-McNabb, Leanne; Zeng, Weiguang; Ede, Nicholas J.; Hourdakis, Irene; Rudd, Michael; Kelso, Anne; Brown, Lorena E. (Cooperative Research Centre for Vaccine Technology, Department of Microbiology and Immunology, University of Melbourne, Parkville, 3052, Australia). International Congress Series, 1219(Options for the Control of Influenza IV), 993-998 (English) 2001. CODEN: EXMDA4. ISSN: 0531-5131. Publisher: Elsevier Science B.V..

AB Background: Lipopeptide **vaccines** contg. minimal CTL determinants have been shown to induce CTL responses against a variety of viruses, however, few have been reported to induce viral clearance. This study examines the ability of a lipopeptide **vaccine** incorporating palmitic acid, a CTL and a helper T cell (TH) determinant from influenza virus, to induce CTL-mediated viral clearing responses. The efficacy of the immunogen was examd. after one or two doses, delivered either in the absence of an adjuvant or formulated with either CFA or Montanide **ISA-720**. Methods: The lipopeptide was administered s.c. (s.c.) to mice and at different times post-priming, mice were challenged with nonlethal doses of influenza virus and the titers in the lungs detd. 5 days later. Results: High levels of anti-viral protection of the lung were achieved when the lipopeptide was administered with or without an adjuvant and only a single dose of **vaccine** was necessary to elicit long-lived immunity. The best redn. in lung virus titers was obtained when the construct was administered in Montanide **ISA-720**. Conclusions: These findings demonstrate the ability of T

cell-based lipopeptide **vaccines** to induce effective influenza viral clearing responses, highlighting their potential as an adjunct to **vaccines** eliciting antibody responses.

L15 ANSWER 12 OF 36 CAPLUS COPYRIGHT 2002 ACS
2001:65584 Document No. 135:179308 Protection of Aotus monkeys by Plasmodium falciparum EBA-175 region II DNA prime-protein boost immunization regimen. Jones, Trevor R.; Narum, David L.; Gozalo, Alfonso S.; Aguiar, Joao; Fuhrmann, Steven R.; Liang, Hong; Haynes, J. David; Moch, J. Kathleen; Lucas, Carmen; Luu, Tin; Magill, Alan J.; Hoffman, Stephen L.; Sim, B. K. L. (Malaria Program, Naval Medical Research Center, Silver Spring, MD, 20910, USA). Journal of Infectious Diseases, 183(2), 303-312 (English) 2001. CODEN: JIDIAQ. ISSN: 0022-1899. Publisher: University of Chicago Press.

AB Aotus monkeys received 4 doses of P. falciparum EBA-175 region II **vaccine** as plasmid DNA (Dv-Dv) or recombinant protein in adjuvant (Pv-Pv) or as 3 doses of DNA and 1 dose of protein (Dv-Pv). After 3 doses, antibody titers were .apprx.104 in DNA-immunized monkeys and 106 in protein-immunized monkeys. A fourth dose did not boost antibody responses in the Dv-Dv only or Pv-Pv only groups, but titers were boosted to .apprx.106 in monkeys in the Dv-Pv group. Four weeks after the last immunization, the animals were challenged with 104 P. falciparum-parasitized erythrocytes. Peak levels of parasitemia were lower in the 16 monkeys that received region II-contg. plasmids or proteins than in the 16 controls. Three of 4 monkeys in the Dv-Pv group did not require treatment. Thus, immunization with EBA-175 region II induces a significant antiparasite effect in vivo.

L15 ANSWER 13 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2001428655 EMBASE Immunological adjuvants in allergy **vaccines**: Past, present and future. Wheeler A.W.; Woroniecki S.R.. Dr. A.W. Wheeler, Allergy Therapeutics Ltd., Dominion Way, Worthing, West Sussex BN14 8SA, United Kingdom. Alan.Wheeler@Allergytherapeutics.com. Allergology International 50/4 (295-301) 2001.
Refs: 50.
ISSN: 1323-8930. CODEN: ALINFR. Pub. Country: Australia. Language: English. Summary Language: English.

AB Hundreds of compounds have been tested over the years in a search for adjuvants to incorporate with antigens or allergens to enhance the immune response. Despite this, aluminum salts have been the only adjuvants that have been both registered for clinical application and used on a large scale until recently. Salts of aluminum, such as aluminum hydroxide, have been used as general immunologic adjuvants for several decades. Some allergen **vaccines** used for the treatment of allergy are still formulated with aluminum-based adjuvants. These formulations have generally proved efficacious and have a good safety profile compared with simple aqueous extracts. However, there is reported sensitivity and toxicity associated with use of aluminum. In addition, aluminum salts are known to be potent stimulators of T helper (h) 2 cell activity. Because Th2 activity directs towards an allergic response, aluminum salts are potentially counterproductive when used as adjuvants in the immunologic treatment of type 1 hypersensitivity. Many soluble and insoluble molecules have been reported to have adjuvant activity in experimental systems. Some of these have been used clinically, but side effects, such as local granuloma formation, have led to their withdrawal from clinical use. Newer depottype adjuvants, such as insoluble calcium salts, tyrosine (now registered) and coupled alginates, may eliminate some of the potential problems of aluminum salts and are currently used in some allergy **vaccines** but have not as yet formed a complete replacement. Liposomes, iscoms and biodegradable microspheres are now being considered for clinical use as adjuvants for both oral and parenteral routes. Soluble adjuvants that are capable of directing the immune response in a more selective way are currently in development for use in allergy

vaccines. One of these, the Th1-directing adjuvant monophosphoryl lipid A (MPL(.RTM.); Corixa, Seattle, WA, USA), is now in clinical use in allergy **vaccines** formulated with the depot adjuvant L-tyrosine. Other ways of stimulating a Th1 response using immunostimulatory DNA sequences (immunostimulatory DNA sequences (ISS) or CpG motifs) as 'built-in' adjuvants are being studied. Further interesting adjuvants reported in the literature, such as Montanide **ISA 720**, SAF-m, RC-529 and QS21, may also be applicable to allergy vaccination.

L15 ANSWER 14 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2001415068 ·EMBASE Malaria **vaccines**: Development of new technologies for immunisation. Genton B.. Dr. B. Genton, Swiss Tropical Institute, Socinstrasse 57, CH-4002 Basel, Switzerland. Blaise.genton@hospvd.ch. CPD Infection 2/3 (102-109) 2001.
Refs: 53.
ISSN: 1468-1668. CODEN: CPDIF3. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB The demonstration of the i) acquired protective immunity in adults living in endemic areas, ii) cure of malaria patients with passive transfer of specific immunoglobulins, and iii) protection conferred by vaccination with sporozoites attenuated by radiation, justifies the search for a malaria **vaccine**. Given the improbability that a **vaccine** directed against a single antigen will be completely protective, the preferred option is to combine several antigens of different stages of the parasite in a multi-component multi-stage **vaccine** which is likely to protect both travellers and populations living in endemic areas. Potential technologies include recombinant proteins, synthetic peptides and DNA **vaccines**, the relevant genes encoding for malaria antigens being inserted into a plasmid or a live vector such as vaccinia or poxvirus. A number of human trials with several antigens and technologies have been carried out in the last ten years. Three **vaccines** have undergone testing in the field in phase IIb or III trials. SPf66, including three synthetic peptides, has been extensively evaluated in different epidemiological settings. The overall efficacy was 23%, and only 2% in African infants, the most susceptible group. The circumsporozoite recombinant protein fused with the antigen S of the hepatitis B virus and formulated in a potent adjuvant (RTS,S) led to a high, but short-term, level or protection against infection and disease in Gambian adults. The first pure asexual blood-stage **vaccine** including three antigens of the merozoite stage (MSP1 & 2 and RESA, Combination B) had an efficacy of 62% to reduce parasite density in Papua New Guinean children. A malaria **vaccine** that can reduce the burden of disease in the most affected populations is thus an achievable goal, each trial providing additional knowledge about mechanisms of protection as well as about **vaccine** technology.

L15 ANSWER 15 OF 36 MEDLINE
2000165116 Document Number: 20165116. PubMed ID: 10699342. Effect of vaccination with 3 recombinant asexual-stage malaria antigens on initial growth rates of Plasmodium falciparum in non-immune volunteers. Lawrence G; Cheng Q Q; Reed C; Taylor D; Stowers A; Cloonan N; Rzepczyk C; Smillie A; Anderson K; Pombo D; Allworth A; Eisen D; Anders R; Saul A. (CRC for Vaccine Technology and Australian Centre for International and Tropical Health and Nutrition, The Queensland Institute of Medical Research and The University of Queensland, Post Office, Royal Brisbane Hospital, Brisbane, Australia.) VACCINE, (2000 Mar 17) 18 (18) 1925-31. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A placebo controlled, randomised, double blind trial was conducted in human volunteers to test a mixture of three recombinant Plasmodium falciparum blood stage antigens for its ability to reduce the initial growth rates of parasites. The **vaccine** contained recombinant MSP2 (3D7 allele), a portion of MSP1 (190LCS.T3) and part of the RESA

antigen (C terminal 771 amino acids) in the Montanide **ISA 720** adjuvant (SEPPIC). Twelve volunteers received two doses of the **vaccine**, 6 weeks apart. The five participants in the placebo group received an equivalent volume of the adjuvant emulsion using the same schedule. Antibody responses were low, as has been reported in earlier studies with this combination, while T cell responses were stronger. All the volunteers were challenged with approximately 140 ring infected red cells of the 3D7 cloned line, 4 weeks after the second dose. Parasitaemia was determined once daily from day 4 using a sensitive and quantitative PCR assay. All the volunteers were infected and were treated on day 8, before any developed symptoms. There was no significant difference in initial parasite growth rates between the verum and placebo groups, nor was there any significant correlation between parasite growth rates and any of the measured immunological responses. These results suggest that the formulation tested in this trial did not generate immune responses that were strong enough to reduce parasite growth in naive volunteers.

L15 ANSWER 16 OF 36 CAPLUS COPYRIGHT 2002 ACS

1999:763900 Document No. 132:11626 CpG oligonucleotides and other adjuvants for inducing mucosal immunity. McCluskie, Michael J.; Davis, Heather L. (Loeb Health Research Institute At the Ottawa Hospital, Can.; CPG Immunopharmaceuticals, Inc.). PCT Int. Appl. WO 9961056 A2 19991202, 116 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US11359 19990521. PRIORITY: US 1998-86393 19980522.

AB The authors disclose the use of immunostimulatory oligonucleotides contg. a CpG motif for inducing mucosal immunity. The CpG immunostimulatory oligonucleotides may be administered alone or in combination with antigen and/or with other adjuvants. In one example, mice were immunized with hepatitis B virus S protein aerosol in conjunction with either cholera toxin or CpG oligonucleotide. A local and systemic IgG response was obsd. using either adjuvant; cholera toxin in combination with CpG oligonucleotide induced a distant mucosal (sIgA) response. In addn., these adjuvants induced a cytotoxic T-cell response to the antigen that was not obsd. on immunization with antigen alone.

L15 ANSWER 17 OF 36 CAPLUS COPYRIGHT 2002 ACS

1999:64824 Document No. 130:138284 Cytotoxic T lymphocyte epitopes from Epstein-Barr virus. Burrows, Scott Renton; Khanna, Rajiv (The Council of the Queensland Institute of Medical Research, Australia; Commonwealth Scientific and Industrial Research Organisation; The University of Melbourne; The Walter and Eliza Hall Institute of Medical Research; CSL Limited; Sherritt, Martina Alison). PCT Int. Appl. WO 9902550 A1 19990121, 73 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-AU531 19980710. PRIORITY: AU 1997-7841 19970710.

AB The present invention provides cytotoxic Epstein-Barr virus (EBV) T-cell epitopes derived from EBV structural antigens. Preferred epitopes include YLLEMLWRL (SEQ ID NO:1), YFLEILWGL (SEQ ID NO:32), YLLEILWRL (SEQ ID NO:33), YLQQNWWTL (SEQ ID NO:6), LLLALLFWL (SEQ ID NO:2), LLVDLLWLL (SEQ ID NO:3), LLLIALWNL (SEQ ID NO:4), WLLLFLAIL (SEQ ID NO:5), TLLVDLLWL (SEQ

ID NO:7), LLWLLLFLA (SEQ ID NO:8), ILLIIALYL (SEQ ID NO:9), VLFIFGCLL (SEQ ID NO:10), RLGATIWQL (SEQ ID NO:11), ILYFIAFAL (SEQ ID NO:15), SLVIVTTFV (SEQ ID NO:17), LMIIPLINV (SEQ ID NO:20), TLFIGSHVV (SEQ ID NO:24), LIPETVPYI (SEQ ID NO:26), VLQWASLAV (SEQ ID NO:27) and QLTPHTKAV (SEQ ID NO:29). The present invention also provides methods of treating or preventing EBV infection in subjects which involve administration of EBV cytotoxic T-cell epitopes. The epitope peptides are useful for treating and preventing nasopharyngeal carcinoma or Hodgkin's disease, and for reducing risk of infectious mononucleosis or post transplantation lymphoproliferative disease.

L15 ANSWER 18 OF 36 CAPLUS COPYRIGHT 2002 ACS
1999:451503 Document No. 131:92494 Adjuvant combination for **vaccines**. Neubert, Andreas; Reuter, Torsten (Impfstoffwerk Dessau-Tornau G.m.b.H., Germany). Ger. Offen. DE 19801834 A1 19990715, 4 pp. (German). CODEN: GWXXBX. APPLICATION: DE 1998-19801834 19980114.

AB **Vaccine** adjuvants made of mineral oil and Al(OH)3 gel as oil-in-water emulsion combinations and process of their prepn. are described. The mineral oil-Al(OH)3 ratios may be 1:0.1 to 0.1:1. The adjuvant can be used for the prepn. of **vaccines** against swine parvovirus, influenza virus, or Erysipelthrix rhusiopathiae. The antigen is first mixed with Al(OH)3 gel for 12 at 4-8.degree.C and then emulsified with mineral oil. A **vaccine** against swine parvovirus was prepd. and tested in pigs and guinea pigs. The **vaccine** with mineral oil and Al(OH)3 adjuvant had superior immunizing properties compared to **vaccines** with Al(OH)3 only or with Al(OH)3-saponin adjuvant.

L15 ANSWER 19 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1999235604 EMBASE A prime-boost regime that combines Montanide ISA720 and Alhydrogel to induce antibodies against the HIV-1 derived multiepitope polypeptide TAB9. Raya N.E.; Quintana D.; Carrazana Y.; Gomez C.E.; Duarte C.A.. N.E. Raya, Division de Formulacion y Envase, Ctro. Ingenieria Genetica/Biotecnol., P.O. Box 6162, Cubanacan, Havana 10600, Cuba. ricardo.silva@cigb.edu.cu. Vaccine 17/20-21 (2646-2650) 4 Jun 1999. Refs: 21.
ISSN: 0264-410X. CODEN: VACCDE.
Publisher Ident.: S 0264-410X(99)00039-0. Pub. Country: United Kingdom.
Language: English. Summary Language: English.

AB A phase I clinical trial with the HIV-1-derived multi-epitope polypeptide (MEP) TAB9 in the oil adjuvant Montanide ISA720 (M-ISA720) was recently performed. Although severe local reactions were reported after the second and third injections of this **vaccine** candidate, the first inoculation was well tolerated. In this article we evaluated a prime-boost regime consisting of one inoculation of TAB9 in M-ISA720 followed by a booster with the same antigen in aluminum hydroxide. This combination of adjuvants elicited similar antibody levels in rabbits than the traditional two-dose schedule with M-ISA720. A control group injected three times with TAB9 in aluminum hydroxide developed markedly lower antibody titers. These results showed that although oil adjuvants are better than alum for priming the immune system for antibody production against TAB9, both kinds of adjuvants can be equally effective in booster immunizations. Therefore, by using the more reactogenic oil adjuvant only for priming, we should be able to eliminate the undesirable reactions characteristic of these compounds while achieving equivalent levels of specific antibodies.

L15 ANSWER 20 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1999170691 EMBASE The V3 loop based multi-epitope polypeptide TAB9 adjuvated with montanide ISA720 is highly immunogenic in nonhuman primates and induces neutralizing antibodies against five HIV-1 isolates. Gomez C.E.; Navea L.; Lobaina L.; Dubed M.; Exposito N.; Soto A.; Duarte C.A.. C.E. Gomez, Departamento de SIDA, Division de Vacunas, Centro Ingeniera Genetica/Biotecnol., Apdo 6162, Playa 10600, Ciudad Habana, Cuba. carlos.duarte@cigb.edu.cu. Vaccine 17/18 (2311-2319) 4 May 1999.

Refs: 24.
ISSN: 0264-410X. CODEN: VACCDE.
Publisher Ident.: S 0264-410X(98)00358-2. Pub. Country: United Kingdom.
Language: English. Summary Language: English.

AB In a previous work we selected montanide ISA720 (M-**ISA 720**) among different adjuvants for the vaccination with a V3 loop based multi-epitope polypeptide TAB9. In this paper we present the evaluation of the toxicity and immunogenicity of this formulation in non-human primates. TAB9 in M-ISA720 was highly immunogenic in macaques (Macaca fascicularis) inducing antibodies against TAB9 in all animals after one inoculation and a strong anamnestic response after booster injections. Furthermore 97% of the V3 peptides included were recognized by TAB9 sera. No differences between doses of 200 .mu.g and 1 mg of TAB9 in M-ISA720 were observed after four immunizations. Neutralizing antibodies against five HIV-1 isolates were detected in most animals. Animals remain healthy throughout the study and did not show lesions at the inoculation site.

L15 ANSWER 21 OF 36 MEDLINE

1999231953 Document Number: 99231953. PubMed ID: 10217601. Peptide based cytotoxic T-cell **vaccines**; delivery of multiple epitopes, help, memory and problems. Elliott S L; Pye S; Le T; Mateo L; Cox J; Macdonald L; Scalzo A A; Forbes C A; Suhrbier A. (Co-operative Research Centre for Vaccine Technology, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Australia.) VACCINE, (1999 Apr 9) 17 (15-16) 2009-19. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Synthetic CD8+ cytotoxic T-lymphocyte (CTL) peptide epitope based **vaccines** are being developed against a number of human diseases. Here we describe extensive preclinical testing of peptide epitope **vaccines** formulated with a protein as a source of CD4 help and Montanide **ISA 720**, an adjuvant currently in human clinical trials. Such water-in-oil formulations could effectively co-deliver several peptide epitopes and simultaneously induce multiple independent CTL responses. The efficiency of CTL induction by some peptides was, however, dependent on the aqueous buffer conditions, with poor performance correlating with non-covalent peptide oligomerisation. Any of a number of proteins currently used in human **vaccines** could supply CD4 help and no difference in CTL induction was obtained if the CD4 response was amnestic or a primary. Peptide immunisation was found to induce long term CTL memory and the recall of protective responses did not depend on an amnestic CD4 response. Slow pyroglutamic acid formation and rapid oxidation of methionine residues was observed in water-in-oil formulations, however, the latter had no effect on CTL induction. These data highlight the need to monitor for potential deleterious chemical events and interpeptide interactions, but illustrate that peptide based vaccination can effectively deliver multiple epitopes, in conjunction with any protein, and induce protective memory.

L15 ANSWER 22 OF 36 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

2001:2453 Document No.: PREV200100002453. Balancing safety and immunogenicity when formulating adjuvanted veterinary **vaccines**: Note I. Tollis, M. (1); Di Pasquale, I. (1); Falcone, E. (1); Vignolo, E. (1); Vivoli, P.. (1) Istituto Superiore di Sanita, Roma Italy. Brown, Fred; Hendriksen, Coenraad F. M.; Sesardic, Dorothea. Developments in Biological Standardization, (1999) Vol. 101, pp. 310. Developments in Biological Standardization. Alternatives to animals in the development and control of biological products for human and veterinary use. print. Publisher: S. Karger AG CH-4009, Basel, Switzerland. Meeting Info.: Symposium on Alternatives to Animals in the Development and Control of Biological Products for Human and Veterinary Use London, England, UK September 24-26, 1998 National Institute for Biological Standards and Control. ISSN: 0301-5149. ISBN: 3-8055-6953-X (paper). Language: English. Summary

Language: English.

L15 ANSWER 23 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1999395203 EMBASE The multi-epitope polypeptide approach in HIV-1 **vaccine** development. Duarte Cano C.A.. C.A. Duarte Cano, Jefe Departamento SIDA, Division de Vacunas, Centro Ingenieria Genetica, Apdo 6162, La Habana 10600, Playa, Cuba. carlos.duarte@cigb.edu.cu. Genetic Analysis - Biomolecular Engineering 15/3-5 (149-153) 1999.
Refs: 15.
ISSN: 1050-3862. CODEN: GEANF4.
Publisher Ident.: S 1050-3862(99)00019-4. Pub. Country: Netherlands.
Language: English. Summary Language: English.

AB The application of a preventive HIV **vaccine** is the only hope for most developing countries to halt the AIDS pandemic. A project aimed to develop a preventive AIDS **vaccine** is being carried out since 1992 by three Cuban research institutions: Centro de Ingenieria Genetica y Biotecnologia de La Habana, Instituto de Medicina Tropical 'Pedro Kouri' and Laboratorio de Investigaciones de SIDA de La Habana. The project includes two main strategies: (a) generation of recombinant multi-epitope polypeptides (MEPs) bearing several copies of the V3 loop from different HIV-1 isolates; and (b) development of immunogens capable of inducing a cytotoxic T cell response (CTL) specific for human immunodeficiency virus type 1 (HIV-1) antigens. This article summarizes the work in the first of these strategies. Based on the sequence of the V3 loop of HIV-1 we constructed a series of MEPs and evaluated their immunogenicity in mice, rabbits and macaques. The MEP TAB9, containing six V3 epitopes from isolates LR10, JY1, RF, MN, BRVA and IIIB, was selected together with the oil adjuvant Montanide ISA720 (SEPPIC, France) to perform a Phase I clinical trial in HIV seronegative Cuban volunteers. The trial was double blinded, randomized, and fulfilled all ethical and regulatory requirements. All TAB9 vaccinated volunteers developed a strong immune response and neutralizing antibodies were observed in the 50% of the subjects. However the second and third inoculations of the **vaccine** were not well tolerated because transient severe local reactions appeared in some individuals. A new formulation of TAB9 is currently in pre-clinical studies and is expected to enter clinical trials in 1999.

L15 ANSWER 24 OF 36 CAPLUS COPYRIGHT 2002 ACS
1999:592512 Document No. 132:92016 Effect of different adjuvants and immunomodulators on the humoral immune response of rabbits and mice against HIV-1-derived multi-epitope polypeptides. Herrera, Antonieta M.; Vazquez, Dania; Navea, Leonor; Lobaina, Leonor; Quintana, Diogenes; Napoles, Annara; Garcia, Yenela; Duarte, Carlos A. (Vaccine Division, AIDS Department, Center for Genetic Engineering and Biotechnology, Havana, 10600, Cuba). Biotecnologia Aplicada, 16(2), 103-108 (English) 1999. CODEN: BTAPEP. ISSN: 0864-4551. Publisher: Sociedad Iberolatinoamericana de Biotecnologia Aplicada a la Salud.

AB The third variable region (V3 loop) of the human immunodeficiency virus (HIV) external glycoprotein gp 120 contains the principal neutralizing domain of this protein. Our group has developed multi-epitope polypeptides (MEP), bearing several copies of the V3 loop from different HIV-1 isolates. These chimeric proteins have been able to elicit broadly reactive neutralizing antibodies when administered in Complete Freund's Adjuvant (CFA). For human **vaccines**, a less reactogenic adjuvant is required. The MEPs TAB9 and TAB13 contain the V3 region from six and eight HIV-1 isolates, resp., fused to the amino terminus of the Neisseria meningitidis P64K protein. In this paper we describe the effect of several adjuvants and immunomodulators on the antibody response against these MEPs in rabbits and mice. Oil adjuvants proved to be more efficient in promoting the antibody response against MEPs than Alum, Quil A or combinations of Alum with IL-2 and .gamma.IFN. The subclass compn. of the antibody response was very dependent on the adjuvant employed. CFA

induced high levels of IgG2a and IgG2b, while for the rest of the products IgG1 was predominant. We also concluded that the novel oil adjuvant Montanide ISA720 is as efficient as CFA or Incomplete Freund's Adjuvant in stimulating the humoral response in mice and rabbits and therefore, it was selected for further studies in primates.

L15 ANSWER 25 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1998267947 EMBASE Candidate **vaccines** for Epstein-Barr virus. Moss D.J.; Suhrbier A.; Elliott S.L.. D.J. Moss, Epstein-Barr virus Unit, Queensland Inst. Medical Research, Brisbane, QLD 4029, Australia. British Medical Journal 317/7156 (423-424) 15 Aug 1998.
Refs: 10.
ISSN: 0959-8146. CODEN: BMJOAE. Pub. Country: United Kingdom. Language: English.

L15 ANSWER 26 OF 36 MEDLINE
97405281 Document Number: 97405281. PubMed ID: 9261951. Selection of an adjuvant for vaccination with the malaria antigen, MSA-2. Pye D; Vandenberg K L; Dyer S L; Irving D O; Goss N H; Woodrow G C; Saul A; Alving C R; Richards R L; Ballou W R; Wu M J; Skoff K; Anders R F. (CSL Ltd., Parkville, Vic., Australia.) VACCINE, (1997 Jun) 15 (9) 1017-23. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Various formulations of the Plasmodium falciparum merozoite surface antigen, MSA-2, were made and tested in animals in order to select one for use in human **vaccine** trials. Recombinant constructs representing both major allelic forms of MSA-2 were formulated with a range of adjuvants and used to immunize rabbits, mice and sheep. After immunization, antibody responses obtained with the most potent adjuvants were at least tenfold greater than responses obtained with the least potent adjuvant Alhydrogel, which was used as the reference standard, although its lower potency indicated against its further use in clinical trials. Based on broadly similar results obtained with the three animal species, several adjuvants, including the water-in-oil adjuvant Montanide **ISA 720**, the oil-in-water adjuvant SAF-1, and liposomes containing lipid A formulated with Alhydrogel were demonstrated to be potent and potentially suitable for the clinical evaluation of MSA-2 as a candidate malaria **vaccine** antigen. Of these, **ISA 720** was selected for further trial.

L15 ANSWER 27 OF 36 MEDLINE
97218598 Document Number: 97218598. PubMed ID: 9066035. Phase I trial in humans of an oil-based adjuvant SEPPIC MONTANIDE **ISA 720** . Lawrence G W; Saul A; Giddy A J; Kemp R; Pye D. (Tropical Health Program, Queensland Institute of Medical Research, Brisbane, Australia.) VACCINE, (1997 Feb) 15 (2) 176-8. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Seppic MONTANIDE **ISA 720** is a metabolizable oil adjuvant that has given good results in animals with recombinant malarial antigens. Twelve human volunteers were given increasing intramuscular doses of MONTANIDE **ISA 720**, ranging from 0.6 to 1.8 ml. The adjuvant was well tolerated with only minor local effects, including tenderness, local swelling and discomfort on use. MONTANIDE **ISA 720** may prove to be an acceptable and effective adjuvant for use in people.

L15 ANSWER 28 OF 36 MEDLINE
97158172 Document Number: 97158172. PubMed ID: 9004444. Vaccination of sheep against larvae of the sheep blowfly (Lucilia cuprina). Bowles V M; Meeusen E N; Young A R; Andrews A E; Nash A D; Brandon M R. (Centre for Animal Biotechnology, School of Veterinary Science, University of Melbourne, Parkville, Victoria, Australia.) VACCINE, (1996 Oct) 14 (14) 1347-52. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND:

United Kingdom. Language: English.

AB Four first stage larval antigens from the sheep blowfly were identified using supernatants from cultures of antibody secreting cells. These partially purified larval antigens, when added to **Montanide ISA-25** containing recombinant ovine IL-1 beta (rovIL-1 beta) were used to successfully vaccinate sheep against larvae of the sheep blowfly. Significantly less strikes were recorded on vaccinated sheep compared to controls ($P < 0.033$) with surviving larvae from vaccinated sheep up to 85% smaller than larvae from control sheep. RovIL-1 beta was found to be an important component of the **vaccine**. Vaccinated sheep showed both humoral and cellular immune responses to the larval antigens. Antibody levels generally correlated directly with delayed-type hypersensitivity (DTH) responses, but neither antibody nor DTH correlated positively with protection in vaccinated sheep. Skin sections removed from individual sheep immediately after challenge revealed aggregations of CD4+, gamma delta-TCR+ and CD1+ cells located directly under the epidermis in vaccinated sheep.

L15 ANSWER 29 OF 36 MEDLINE

97120834 Document Number: 97120834. PubMed ID: 8961504. International bank for foot-and-mouth disease **vaccine**: assessment of **Montanide ISA 25** and ISA 206, two commercially available oil adjuvants. Barnett P V; Pullen L; Williams L; Doel T R. (Institute for Animal Health, Pirbright Laboratory, Woking, Surrey, UK.) VACCINE, (1996 Sep) 14 (13) 1187-98. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The International **Vaccine** Bank at Pirbright has recently installed large-scale **vaccine** formulation equipment for the preparation of oil-adjuvanted **vaccines**. Such **vaccines** are claimed to offer a number of advantages over Al(OH)3, particularly their ability to raise better immunity in pigs. This paper reports on the potency in pigs, cattle and guinea-pigs of foot-and-mouth disease **vaccines** prepared with two novel oil adjuvants, **Montanide ISA 25** and 206 (Seppic, Paris). The results indicate that **vaccines** adjuvanted with these oils retain potency for a longer period than our conventional aqueous formulation, following storage at +4 degrees C, and elicit good antibody responses in both pigs and cattle regardless of injection route. In addition they gave no evidence of toxicity or prolonged pyrexia following their administration. Local reactions at the site of inoculation were not observed in cattle vaccinated intramuscularly, even following a booster dose. Pigs vaccinated intramuscularly only showed local reactions if the volume administered exceeded the 2.0 ml dose or the animals received a second vaccination. These observations on the efficacy of such oil formulated **vaccines** suggest that they have potential as an alternative to the current aqueous formulation.

L15 ANSWER 30 OF 36 CAPLUS COPYRIGHT 2002 ACS

1996:438749 Document No. 125:112255 Comparison of adjuvant formulations for cytotoxic T cell induction using synthetic peptides. Hioe, Catarina E.; Qiu, Howard; Chend, Pei-De; Bian, Zuning; Li, Ming-Lie; Li, Joseph; Singh, Manmohan; Kuebler, Peter; McGee, Paul; et al. (Department Pathology, New York University, New York, NY, 10010, USA). Vaccine, 14(5), 412-418 (English) 1996. CODEN: VACCDE. ISSN: 0264-410X. Publisher: Elsevier.

AB We have investigated the capacity of synthetic peptides delivered in different adjuvant formulations to induce cytotoxic T lymphocyte (CTL) responses to a class I H-2Kd-restricted Plasmodium berghei circumsporozoite epitope, CS 252-260. Using three immunogen formulations: soybean emulsion; Montanide ISA720; and lipopeptide (P3-CS), we first evaluated the effects of immunization routes on CTL induction. No CTL response was induced in mice immunized s.c. or i.p. with CS peptide formulated in soybean emulsion. In contrast, immunization with lipopeptide P3-CS either s.c. or i.p. effectively primed for CTL.

Interestingly, CS peptide emulsified in Montanide ISA720 induced a CTL response only when delivered s.c. and not i.p., indicating the crit. influence of immunization routes on CTL induction. We then compared the effectiveness of eight adjuvant formulations to induce CTL response following a single s.c. immunization. Notably, lipopeptide P3-CS and CS peptide admixed with P3 or POE lipid mols. stimulated a vigorous CTL response. However, only mice immunized with P3-CS and CS peptide admixed with P3 mol. generated long-lived CTL which persisted in vivo for 5 mo. Thus, based on a simultaneous comparison of the different adjuvant formulations, we demonstrated that the conjugated and unconjugated P3 lipopeptides were the most effective immunogens for eliciting primary and memory CTL in mice.

L15 ANSWER 31 OF 36 CAPLUS COPYRIGHT 2002 ACS
1995:958292 Document No. 123:350258 Injectable emulsion formulations for administration of plasmids in **vaccines** and therapeutics. Ganne, Vincent (Societe d'Exploitation de produits pour l'Industrie Chimique, (S.E.P.P.C.), Fr.). PCT Int. Appl. WO 9525542 A1 19950928, 21 pp. DESIGNATED STATES: W: JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (French). CODEN: PIXXD2. APPLICATION: WO 1995-FR345 19950321. PRIORITY: FR 1994-3361 19940322.
AB Injectable emulsions (oil-in-water, water-in-oil, water-in-oil-in-water) suitable for the administration of plasmid expression vectors for use in vector **vaccines** or gene therapy are described. Typically, the emulsions have a viscosity of 300 mPA.s. A series of formulations using oil-in-water and water-in-oil emulsions using combinations of Montanide oils and Avridine were used to administer expression vectors carrying the GP50 gene of pseudorabies virus to mice. **Vaccines** using Montanide ISA25 in the oil phase led to higher titers of antibody (32-1024) than prior art formulations (<8-32).

L15 ANSWER 32 OF 36 CAPLUS COPYRIGHT 2002 ACS
1995:851987 Document No. 123:254563 Ectoparasite antigens and their use in **vaccines**. Brandon, Malcolm Roy; Bowles, Vernon Morrison (University of Melbourne, Australia; Australian Wool Research and Promotion Organisation). PCT Int. Appl. WO 9522603 A1 19950824, 44 pp. DESIGNATED STATES: W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UG; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1995-AU78 19950217. PRIORITY: AU 1994-3923 19940217; AU 1994-3999 19940221; AU 1994-8770 19941013.
AB Antigens for preventing or reducing ectoparasite infection or disease in an animal are described. **Vaccines** including the antigens, an adjuvant and a cytokine are described. Specifically, sheep blowfly antigens are identified for use in **vaccines**. The antigens were identified as cross-reacting with antibody-contg. supernatants from cultures of lymphocytes from peripheral lymph nodes of sheep infected under controlled conditions. Four major surface antigens were identified and two of them were glycoproteins. Larvae grown in the presence of the antibody grew more slowly than controls. N-terminal sequences of immunoaffinity purified antigens were obtained. In vivo tests indicated that a combination of all four major antigens gave significant protection against challenge with sheep blowfly with infection unusual (11% of all attempts were successful) and with larvae stunted (85% inhibition of growth). Effectiveness of the antigens was increased by incorporating interleukin 1.beta. into the **vaccine**.

L15 ANSWER 33 OF 36 MEDLINE
95115095 Document Number: 95115095. PubMed ID: 7815511. Induction of protective cytotoxic T cells to murine cytomegalovirus by using a nonapeptide and a human-compatible adjuvant (Montanide **ISA**

720). Scalzo A A; Elliott S L; Cox J; Gardner J; Moss D J; Suhrbier A. (Department of Microbiology, University of Western Australia, Queen Elizabeth II Medical Centre, Nedlands.) JOURNAL OF VIROLOGY, (1995 Feb) 69 (2) 1306-9. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The use of synthetic peptides representing cytotoxic T-cell (CTL) epitopes for human vaccination requires the identification of a suitable adjuvant formulation. A single immunization with Montanide ISA720/tetanus toxoid/YPHFMPTNL protected mice against murine cytomegalovirus and induced epitope-specific CTL. Such formulations will find application in peptide-based CTL anti-viral **vaccines**.

L15 ANSWER 34 OF 36 CAPLUS COPYRIGHT 2002 ACS

1994:638392 Document No. 121:238392 Recombinant living subunit **vaccine** combined with an injectable emulsion. Ganne, Vincent (Societe d'Exploitation de Produits Pour les Industries Chimiques, S.E.P.P.I.C, Fr.). PCT Int. Appl. WO 9416681 A1 19940804, 39 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (French). CODEN: PIXXD2. APPLICATION: WO 1994-FR106 19940128. PRIORITY: FR 1993-942 19930129.

AB Recombinant living **vaccine** compn. comprising a recombinant subunit **vaccine** combined with an injectable emulsion. **Vaccines** contg. recombinant adenovirus gp50 75, and **Montanide ISA 25** 25% were tested for their ability to induce antibody against gp50.

L15 ANSWER 35 OF 36 CAPLUS COPYRIGHT 2002 ACS

1995:187317 Document No. 122:7358 Enhancement of the efficacy of a replication-defective adenovirus-vectored **vaccine** by the addition of oil adjuvants. Ganne, V.; Eloit, M.; Laval, A.; Adam, M.; Trouve, G. (SEPPIC, Paris, 75321, Fr.). Vaccine, 12(13), 1190-6 (English) 1994. CODEN: VACCDE. ISSN: 0264-410X.

AB We previously constructed a recombinant adenovirus with a defective E1A gene, which expresses high levels of the pseudorabies virus gp50 in non-transcomplementing cells. The virus is unable to replicate in mice. It elicited the prodn. of anti-gp50 antibodies only when high concns. (108 TCID50 per dose) of the virus were used and it gave mice little protection. The combination of the recombinant adenovirus at several concns. (108, 107.4, 106.4 TCID50 per dose) with certain oil adjuvants in different galenic forms (water-in-oil, oil-in-water, water-in-oil-in-water) led to an increase in specific antibody responses and protection for the host when challenged with a virulent pseudorabies virus under very severe conditions, i.e. where 100% of unvaccinated mice died. A water-in-oil-in-water formulation induced a very high level of anti-gp50 antibodies even with a low concn. of adenovirus. These results could be correlated to the induction of cytokines, such as IL6, which is obsd. with this galenic form. The oil-adjuvanted emulsions induced IL2, suggesting that they were able to activate T-helper cells. Different oil formulations elicited the different IgG subclasses (IgG1, IgG2a, IgG2b, IgG3). These results can be extended to other live replication-defective **vaccines** expressing different proteins.

L15 ANSWER 36 OF 36 MEDLINE

95109843 Document Number: 95109843. PubMed ID: 7810803. Protective immunity induced in squirrel monkeys with recombinant apical membrane antigen-1 of Plasmodium fragile. Collins W E; Pye D; Crewther P E; Vandenberg K L; Galland G G; Sulzer A J; Kemp D J; Edwards S J; Coppel R L; Sullivan J S; +. (Division of Parasitic Diseases, Centers for Disease Prevention & Control, Atlanta, Georgia.) AMERICAN JOURNAL OF TROPICAL MEDICINE AND HYGIENE, (1994 Dec) 51 (6) 711-9. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB Saimiri sciureus boliviensis monkeys were immunized with the Plasmodium fragile form of the merozoite apical membrane antigen-1 produced using the

baculovirus expression system and combined with Montanide **ISA 720** adjuvant. Following three immunizations, monkeys were challenged with 10,000 P. fragile trophozoite parasites. Antibody titers determined by fluorescence microscopy indicated an enhanced response following the second immunization. Four of five control animals had parasite counts > 5% 18-26 days following challenge. Four of five immunized monkeys had reduced levels of maximum parasitemia or delays in accumulated parasite counts, suggestive of protection. Rechallenge of the animals with P. falciparum resulted in three of four adjuvant control animals developing patent parasitemia whereas none of five immunized animals were infected, suggesting some level of heterologous protection.

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     09 OCT 2002
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L2           512 S L1 AND SQUALANE
L3            95 S L2 AND EMULSION
L4             3 S L3 AND STORAGE
L5             3 DUP REMOVE L4 (0 DUPLICATES REMOVED)
L6            23 S L3 AND COMPOSITION
L7             2 S L6 AND IMMUNOGENIC
L8             2 DUP REMOVE L7 (0 DUPLICATES REMOVED)
L9             2 S MONTANIDE ISA 703
L10            2 DUP REMOVE L9 (0 DUPLICATES REMOVED)
L11            0 S MONANIDE ISA 25
L12           78 S MONTANIDE ISA 25 OR ISA 703 OR ISA 719 OR ISA 720
L13           42 DUP REMOVE L12 (36 DUPLICATES REMOVED)
L14           36 S L13 AND VACCINE
L15           36 DUP REMOVE L14 (0 DUPLICATES REMOVED)

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L20            3 DUP REMOVE L19 (8 DUPLICATES REMOVED)

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L20  ANSWER 1 OF 3     MEDLINE                                DUPLICATE 1
2002070731  Document Number: 21655403.    PubMed ID: 11796000.   Endothelin
     receptor A blockade ameliorates hypothermic ischemia-reperfusion-related
     microhemodynamic disturbances during liver transplantation in the rat.
     Zhang Xing-yi; Francis Richard J B; Sun Ck Cheuk-kwan; Wheatley Antony M.
     (Microcirculation Research Laboratory, University of Otago, Dunedin, New
     Zealand. ) JOURNAL OF SURGICAL RESEARCH, (2002 Feb) 102 (2) 63-70.
     Journal code: 0376340. ISSN: 0022-4804. Pub. country: United States.
     Language: English.
AB   BACKGROUND: The objective of this study was to investigate the effect of
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graft treatment with specific endothelin receptor antagonists (ET(A) and ET(B)) on the microhemodynamic disturbances which occur following ischemia/reperfusion injury during orthotopic liver transplantation (OLT) in the rat. MATERIALS AND METHODS: OLT was performed in male Sprague-Dawley rats. An ET(A) receptor antagonist (BQ-610; 0.3 mg/kg) or ET(B) receptor antagonist IRL-1038 (20 nmol/kg) was administered intraportally into liver grafts in vitro at the beginning of 2- and 6-h **cold storage** (**4 degrees** C) using physiological saline. Sham-operated animals served as controls (Cont). Seven groups were studied: Cont; **vehicle**-2 h (saline treated); ET(B) antagonist-2 h; ET(A) antagonist-2 h; **vehicle**-6 h; ET(A) antagonist-6 h; and ET(B) antagonist-6 h. At 1 h after graft implantation, the liver microcirculation was investigated by intravital fluorescence microscopy. RESULTS: In **vehicle**-treated livers, the hepatic microcirculation was markedly impaired compared with the Cont as manifested by a reduced lobular perfusion index, increased incidence of sinusoidal nonperfusion, elevated leukocyte adhesion in sinusoids and terminal hepatic venules, and increased hepatic venous resistance (23-fold; 6-h group). In addition, plasma liver enzymes were significantly elevated in the **vehicle** treated groups. Alterations to all these parameters were markedly reduced in the ET(A) receptor antagonist-treated liver grafts although there was still evidence of hepatic injury. The ET(B) receptor antagonist had little effect on the I/R-induced changes to the hepatic microcirculation. CONCLUSIONS: Our results indicate that the ET(A) antagonism ameliorates hypothermic I/R-related microhemodynamic disturbances during OLT in the rat, suggesting that application of an ET(A) antagonist to liver grafts may have therapeutic potential in human liver transplantation.

L20 ANSWER 2 OF 3 MEDLINE DUPLICATE 2
2000168557 Document Number: 20168557. PubMed ID: 10706040. Donor treatment with mycophenolate mofetil: protection against ischemia-reperfusion injury in the rat. Valentin J F; Bruijn J A; Paul L C. (Department of Medicine, University of Toronto at St. Michael's Hospital, Ontario, Canada.) TRANSPLANTATION, (2000 Feb 15) 69 (3) 344-50. Journal code: 0132144. ISSN: 0041-1337. Pub. country: United States. Language: English.
AB BACKGROUND: Mycophenolic acid, the active metabolite of mycophenolate mofetil, inhibits the glycosylation of cell membrane glycoproteins. We hypothesized that impaired glycosylation of cell adhesion molecules on endothelial cells in vivo results in decreased susceptibility to inflammation or immunogenicity after allogeneic transplantation. METHODS: The expression of mannose residues on cultured rat endothelial cells was examined after stimulation with interleukin 1 in the presence or absence of mycophenolic acid using labeled Galanthus nivalis agglutinin. The in vitro adhesion of blood leukocytes to heart tissue was examined using peripheral blood leukocytes of recipient origin and sections of donor heart tissue exposed to ischemia-reperfusion injury after pretreatment with **vehicle** or mycophenolic mofetil. (LEWxBN)F1 donor rats were treated with 20 or 60 mg/kg/day of mycophenolate mofetil for 1 or 2 weeks followed by transplantation of the heart into Lewis recipients after storage in heparin-containing normal saline for either 10 min at **4 degrees** C or 120 min at room temperature. RESULTS: Endothelial cells stimulated in vitro with interleukin 1 showed an increase in a population of strongly mannose-positive cells, which was prevented by the addition of mycophenolic acid during the culture. The in vitro adhesion of peripheral blood leukocytes to cardiac tissue sections exposed to prolonged storage and reperfusion was significantly less if the donor had been treated with mycophenolate mofetil. Treatment of cardiac graft donors with mycophenolate mofetil protected the graft against early graft failure after prolonged storage at room temperature, because the mean graft survival was 9.4+/-0.6 days for grafts that came from donors treated with

mycophenolate mofetil versus 1.2+/-0.9 days (P<0.05) for grafts that came from **vehicle**-treated donors. Donor pretreatment with mycophenolate mofetil did not affect the survival time of heart grafts transplanted after 15 min of standard **cold storage** or the survival of grafts transplanted into presensitized recipients. CONCLUSION: Donor treatment with mycophenolate mofetil protects cardiac grafts against primary nonfunction after prolonged tepid storage, which may be related to the inhibition of glycosylation of cell adhesion molecules involved in ischemia-reperfusion injury.

L20 ANSWER 3 OF 3 MEDLINE DUPLICATE 3
94208272 Document Number: 94208272. PubMed ID: 8156795. Cryopreservation of the mammalian kidney. I. Transplantation of rabbit kidneys perfused with EC and RPS-2 at 2-**4 degrees** C. Khirabadi B S; Fahy G M. (Transplantation Laboratory, American Red Cross Biomedical R&D, Rockville, MD 20855.) CRYOBIOLOGY, (1994 Feb) 31 (1) 10-25. Journal code: 0006252. ISSN: 0011-2240. Pub. country: United States. Language: English.

AB The requirements of organ cryopreservation differ from those of conventional organ preservation. The encouraging results of Karow's group with dog kidneys transplanted after perfusion with more than 4 M dimethyl sulfoxide were based on an RPS-2 (renal preservation solution 2) **vehicle** solution, but transplantation of rabbit kidneys after perfusion with RPS-2 has not been reported. We evaluated RPS-2 in comparison to Euro-Collins solution (EC) using a modified technique for rabbit kidney autotransplantation and a computer-based organ perfusion machine designed for the introduction and removal of cryoprotective agents. Consistent success in rabbit kidney transplantation was found to depend on the anesthetic used, the hydration volumes administered, and direct ureter-to-ureter anastomosis. RPS-2 was found to be equivalent to EC for short-term (about 5 h) preservation by either perfusion or simple **cold storage**. However, good results with EC were associated with perfusion at **4 degrees** C, recovery being significantly worse at 2 degrees C. In addition, we found that the solitary rabbit kidney is not able to fully compensate for the loss of the contralateral kidney, the result being persistent (to 3 weeks) mild elevation of serum creatinine, potassium, and calcium and persistent moderate reduction of serum phosphate. These results establish perfusates, perfusion conditions, transplantation techniques, computer-based perfusion control techniques, and a general clinical baseline that are permissive of further direct experiments on cryoprotectant introduction and removal.

=> s gastrin 17
L21 2085 GASTRIN 17

=> s l21 and conjugate
L22 20 L21 AND CONJUGATE

=> s l22 and oily vehicle
L23 1 L22 AND OILY VEHICLE

=> d l23 cbib abs

L23 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
2001:472459 Document No. 135:66189 A stable immunogenic composition for frozen storage containing protein carriers. Grimes, Stephen; Blackburn, Peter (Aphton Corporation, USA). PCT Int. Appl. WO 2001045670 A2 20010628, 48 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,

ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US35248 20001222. PRIORITY: US 1999-PV173022 19991223.

AB An injectable vaccine compn. comprising an immunogenic **conjugate** in an emulsion contg. advantageous **oily vehicles** is disclosed as suitable for frozen storage; moreover, a water-in-oil emulsion compn. is found to enhance immunogenicity after storage at about -18.degree.. For example, an aq. phase droplets of an anti-gastrin immunogenic emulsion (e.g., human **gastrin 17**(1-9)Ser 9-diphtheria toxoid **conjugate**) were stable at -70.degree., -18.degree., and 4.degree., but less stable at 25.degree.. The **conjugate** purity was most stable at -70.degree. and -18.degree., less stable at 4.degree. and much less stable at 25.degree.. The behavior in the release assay was not altered by storage at any four select temps. The immunogenicity response was unaffected by storage at 4.degree.. Storage at -18.degree. increased immunogenicity. The finding that it was possible to enhance immunogenicity by a single freeze-thaw cycle (freezing at -18.degree.) was unexpected. Although storage at -70.degree. and 25.degree. resulted in more variable responses, there was no clear trend that might be predictive for length of feasible storage time; in addn., immunogenicity was not altered from the time 0 control. However, not all emulsion formulations showed the stable storability according to this invention. Accordingly, the emulsions capable of withstanding freezing have been found to include Montanide ISA 25, 703, 719, and 720.

=> s l22 and Montanide ISA
L24 1 L22 AND MONTANIDE ISA

=> d l24 cbib abs

L24 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
2001:472459 Document No. 135:66189 A stable immunogenic composition for frozen storage containing protein carriers. Grimes, Stephen; Blackburn, Peter (Aphton Corporation, USA). PCT Int. Appl. WO 2001045670 A2 20010628, 48 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US35248 20001222. PRIORITY: US 1999-PV173022 19991223.

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showed the stable storability according to this invention. Accordingly, the emulsions capable of withstanding freezing have been found to include **Montanide ISA** 25, 703, 719, and 720.

=> dup remove l22
PROCESSING COMPLETED FOR L22
L25 17 DUP REMOVE L22 (3 DUPLICATES REMOVED)

=> d l25 1-17 cbib abs

L25 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2002 ACS
2002:332011 Document No. 136:355482 Compositions comprising a polypeptide and an active agent. Piccariello, Thomas; Olon, Lawrence P.; Kirk, Randall J. (New River Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2002034237 A1 20020502, 98 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US26142 20010822. PRIORITY: US 2000-642820 20000822.
AB Claimed are compns. comprising a polypeptide and an active agent covalently attached to the polypeptide and a method for delivery of an active agent to a patient by administering the compn. to the patient. The peptide is a homopolymer of a naturally occurring amino acid or a heteropolymer of two or more naturally occurring amino acids. In an example, (Glu)n-cephalexin was prepd. from Glu(OBut)NCA and cephalexin hydrochloride.

L25 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2002 ACS
2002:556104 Document No. 137:109489 Compositions comprising a polypeptide and an active agent. Piccariello, Thomas; Olon, Lawrence P.; Kirk, Randal J. (USA). U.S. Pat. Appl. Publ. US 2002099013 A1 20020725, 34 pp. (English). CODEN: USXXCO. APPLICATION: US 2001-933708 20010822. PRIORITY: US 2000-PV247928; 20001114; US 2000-PV247621; 20001114; US 2000-PV247620; 20001114; US 2000-PV247595; 20001114; US 2000-PV247594; 20001114; US 2000-PV247635; 20001114; US 2000-PV247634; 20001114; US 2000-PV247606; 20001114; US 2000-PV247607; 20001114; US 2000-PV247608; 20001114; US 2000-PV247609; 20001114; US 2000-PV247610; 20001114; US 2000-PV247611; 20001114; US 2000-PV247702; 20001114; US 2000-PV247701; 20001114; US 2000-PV247700; 20001114; US 2000-PV247699; 20001114; US 2000-PV247698; 20001114; US 2000-PV247807; 20001114; US 2000-PV247833; 20001114.
AB Claimed are compns. comprising a polypeptide and an active agent covalently attached to the polypeptide and a method for delivery of an active agent to a patient by administering the compn. to the patient. The peptide is a homopolymer of a naturally occurring amino acid or a heteropolymer of two or more naturally occurring amino acids. In an example, (Glu)n-cephalexin was prepd. from Glu(OBut)NCA and cephalexin hydrochloride.

L25 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2002 ACS
2001:472459 Document No. 135:66189 A stable immunogenic composition for frozen storage containing protein carriers. Grimes, Stephen; Blackburn, Peter (Aphton Corporation, USA). PCT Int. Appl. WO 2001045670 A2 20010628, 48 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,

ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US35248 20001222. PRIORITY: US 1999-PV173022 19991223.

AB An injectable vaccine compn. comprising an immunogenic **conjugate** in an emulsion contg. advantageous oily vehicles is disclosed as suitable for frozen storage; moreover, a water-in-oil emulsion compn. is found to enhance immunogenicity after storage at about -18.degree.. For example, an aq. phase droplets of an anti-gastrin immunogenic emulsion (e.g., human **gastrin 17**(1-9)Ser 9-diphtheria toxoid **conjugate**) were stable at -70.degree., -18.degree., and 4.degree., but less stable at 25.degree.. The **conjugate** purity was most stable at -70.degree. and -18.degree., less stable at 4.degree. and much less stable at 25.degree.. The behavior in the release assay was not altered by storage at any four select temps. The immunogenicity response was unaffected by storage at 4.degree.. Storage at -18.degree. increased immunogenicity. The finding that it was possible to enhance immunogenicity by a single freeze-thaw cycle (freezing at -18.degree.) was unexpected. Although storage at -70.degree. and 25.degree. resulted in more variable responses, there was no clear trend that might be predictive for length of feasible storage time; in addn., immunogenicity was not altered from the time 0 control. However, not all emulsion formulations showed the stable storability according to this invention. Accordingly, the emulsions capable of withstanding freezing have been found to include Montanide ISA 25, 703, 719, and 720.

L25 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2002 ACS

2000:777066 Document No. 134:96835 Stabilization of a tyrosine O-sulfate residue by a cationic functional group: formation of a **conjugate** acid-base pair. Yagami, T.; Kitagawa, K.; Aida, C.; Fujiwara, H.; Futaki, S. (National Institute of Health Sciences, Tokyo, Japan). Journal of Peptide Research, 56(4), 239-249 (English) 2000. CODEN: JPERFA. ISSN: 1397-002X. Publisher: Munksgaard International Publishers Ltd..

AB Sulfated tyrosine [Tyr(SO3H)]-contg. peptides showed characteristic peak patterns in their liq. secondary-ion mass spectrometry (LSIMS) spectra. Protonated mols. were desulfated more easily than their deprotonated counterparts. Therefore, the stabilities of the Tyr(SO3H) residues were well-reflected by peak patterns in their pos.-ion spectra. These intrinsic peak patterns were investigated by comparing the behavior of each Tyr(SO3H) residue in acidic soln. As the peptide chain was lengthened and the no. of cationic functional groups increased, the peak representing the [MH]+ of a Tyr(SO3H)-contg. peptide became more prominent than that representing the desulfated [MH-SO3]+. These alterations in peptide structure also increased the stability of the Tyr(SO3H) residue in acidic soln. Based on the desulfation mechanism of an aryl monosulfate, we predicted that intramol. cationic functional groups would stabilize Tyr(SO3H) residues by forming **conjugate** acid-base pairs (or salt bridges) both in the gaseous phase and in acidic soln. In accordance with this theory, Arg residues would take primary responsibility for this self-stabilization within Tyr(SO3H)-contg. peptides. Moreover, a long peptide backbone was expected to have a weak protective effect against desulfation of the [MH]+ in the gaseous phase. Tyr(SO3H) residues were also stabilized by adding an external basic peptide contg. multiple Arg residues. Formation of such intermol. acid-base pairs was demonstrated by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOFMS) which detected conjugated peptide ions. The energetically favorable formation of **conjugate** acid-base pairs prompted by Tyr(SO3H) residues might be a driving force for protein folding and protein-protein interaction.

L25 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2002 ACS

1999:753110 Document No. 131:350281 Immunological control of hypergastrinemia. Gevas, Philip C.; Grimes, Stephen; Karr, Stephen;

Michaeli, Dov; Watson, Susan (Aphton Corporation, USA). PCT Int. Appl. WO 9959631 A1 19991125, 44 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US10751 19990514. PRIORITY: US 1998-85714 19980515.

AB Serum-assocd. hypergastrinemia is treated by administration of gastrin active or passive immunization. An anti-gastrin immunogenic compn. comprising a gastrin G17 or G34 peptide fragment which is amino acid spacer-linked to an immunogenic carrier, is administered to effectively neutralize the circulating gastrin hormone, and moreover, inhibit autocrine activity by progastrin such as Gly-extended G17, and amidated G17, in patients with pernicious anemia. Moreover, the method includes administration of a therapeutically effective amt. of anti-G17 or anti-G34 antibodies which may be in humanized form. Finally, the method provides ameliorating treatment of hypergastrinemic effects of proton pump inhibitors or H2 histamine receptor blocking agents or antagonists, in addn. to treatment of hypergastrinemia caused by diseases such as pernicious anemia.

L25 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2002 ACS

1999:753108 Document No. 132:439 Anti-heptadecagastrin immunogenic compn. immunization in combination with the administration of chemotherapeutic agents for the treatment of gastrin-dependent tumors. Gevas, Philip C.; Grimes, Stephen; Karr, Stephen L.; Watson, Susan A.; Michaeli, Dov (Aphton Corporation, USA). PCT Int. Appl. WO 9959628 A2 19991125, 25 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US10750 19990514. PRIORITY: US 1998-85687 19980515.

AB The invention relates to a combination therapy method for treating gastrin-dependent tumors. The method comprises the immunization of a patient with an anti-heptadecagastrin immunogenic compn. in combination with the administration of chemotherapeutic agents such as 5-fluorouracil and leucovorin.

L25 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2002 ACS

1999:753096 Document No. 132:452 Method for the treatment of gastroesophageal reflux disease using anti-gastrin immunogenic compn. immunization combination with H2 antagonist or proton pump inhibitor. Gevas, Philip C.; Grimes, Stephen; Karr, Stephen; Michaeli, Dov (Aphton Corporation, USA). PCT Int. Appl. WO 9959612 A1 19991125, 24 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US10734 19990514. PRIORITY: US 1998-85610 19980515.

AB A method for the treatment of gastroesophageal reflux disease comprises a combination of active immunization with an anti-gastrin immunogenic compn. with an antagonist which blocks or inhibits the gastric acid pump

activity; or alternatively administering purified anti-gastrin antibodies with a H2 antagonist or proton pump inhibitor of the gastric acid producing enzyme system.

L25 ANSWER 8 OF 17 CAPLUS COPYRIGHT 2002 ACS
1999:402924 Document No. 131:225550 Radiolabeled peptides for targeting cholecystokinin-B/gastrin receptor-expressing tumors. Behr, Thomas M.; Jenner, Niels; Behe, Martin; Angerstein, Christa; Gratz, Stefan; Raue, Friedhelm; Becker, Wolfgang (Department of Nuclear Medicine, Georg-August-University, Gottingen, D-37075, Germany). Journal of Nuclear Medicine, 40(6), 1029-1044 (English) 1999. CODEN: JNMEAQ. ISSN: 0161-5505. Publisher: Society of Nuclear Medicine, Inc..
AB The high sensitivity of pentagastrin stimulation in detecting primary or metastatic medullary thyroid cancer (MTC) suggests widespread expression of the corresponding receptor type on human MTC. Indeed, autoradiog. studies have demonstrated cholecystokinin (CCK)-B/gastrin receptors not only in more than 90% of MTCs but also in a high percentage of small cell lung cancers, some ovarian cancers, astrocytomas and potentially a variety of adenocarcinomas. The aim of this study was to systematically screen and optimize, in a preclin. model and a pilot clin. study, suitable radioligands for targeting CCK-B receptors in vivo. A variety of CCK/gastrin-related peptides, all bearing the C-terminal CCK receptor-binding tetrapeptide sequence Trp-Met-Asp-PheNH2 or derivs. thereof, were studied. They were radioiodinated by the Iodogen or Bolton-Hunter procedures. The peptides were members of the gastrin or CCK families, which differ by the intramol. position of a tyrosyl moiety. Their stability and affinity were studied in vitro and in vivo; their biodistribution and therapeutic efficacy were tested in nude mice bearing s.c. human MTC xenografts. Diethylenetriamine pentaacetic acid (DTPA) derivs. of suitable peptides were synthesized successfully, and their preclin. and initial clin. evaluations were performed, labeled with 111In. All members of the CCK or gastrin families were stable in serum (with half-lives of several hours at 37.degree.C); nevertheless, the stability of those peptides bearing N-terminal pGlu residues or D-amino acids was significantly higher. In accordance with their comparably low affinity, nonsulfated members of the CCK family showed fairly low uptake in the tumor and other CCK-B receptor-expressing tissues. Sulfated CCK derivs. performed significantly better but also displayed a comparably high uptake in normal CCK-A receptor-expressing tissues. This effect was probably due to their similar affinity for both CCK-A and CCK-B receptors. Best tumor uptake and tumor-to-nontumor ratios were obtained with members of the gastrin family because of their selectivity and affinity for the CCK-B receptor subtype. Pilot therapy expts. in MTC-bearing animals showed significant antitumor efficacy compared with untreated controls. DTPA derivs. of minigastrin were successfully developed. In a pilot clin. study, radioiodinated and 111In-labeled derivs. showed excellent targeting of physiol. CCK-B receptor-expressing organs, as well as all known tumor sites. CCK/gastrin analogs may be a useful new class of receptor-binding peptides for diagnosis and therapy of CCK-B receptor-expressing tumors, such as MTC or small cell lung cancer. Nonsulfated gastrin derivs. may be preferable because of their CCK-B receptor selectivity, hence lower accretion in normal CCK-A receptor-expressing organs.

L25 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2002 ACS
1998:155847 Document No. 128:278696 Pre-clinical evaluation of the Gastrimmune immunogen alone and in combination with 5-fluorouracil/leucovorin in a rat colorectal cancer model. Watson, Susan A.; Michael, Dov; Justin, Timothy A.; Grimes, Stephen; Morris, Teresa M.; Robinson, Graham; Clarke, Philip A.; Hardcastle, Jack D. (Cancer Studies Unit, Department of Surgery, University Hospital, University of Nottingham, Nottingham, UK). International Journal of Cancer, 75(6), 873-877 (English) 1998. CODEN: IJCNAW. ISSN: 0020-7136. Publisher: Wiley-Liss, Inc..

AB Mature and post-translational precursor gastrin forms are growth factors for colorectal tumors. The immunogen Gastrimmune is composed of the amino terminus of **gastrin-17** linked to diphtheria toxoid and raises antibodies in situ which neutralize amidated and glycine-extended **gastrin-17**. The aim of the study was to det. the effect of treatment with 5-fluorouracil(5-FU)/leucovorin on the antibody titers induced by Gastrimmune and the effect of combination therapy on the growth of the rat colon tumor DHDK12. Gastrimmune was administered to rats s.c. at 3 weekly intervals. The rat colon tumor line DHDK12 was injected into the abdominal wall of BDIX rats. Combinations of 5-FU/leucovorin were injected i.v. on days 1, 3 and 5, with the cycle repeated every 4 wk. Antibody titers were measured by an ELISA technique. Antibody titers were followed for 40 wk after Gastrimmune (500 .mu.g .cntdot.mL-1) immunization, with titers peaking between 10 and 20 wk after a single immunization and falling by week 30. At termination, no effect was obsd. on either the histol. appearance of the gastro-intestinal tract or the proliferation of the colonic mucosa. Pre- and post-treatment with 5-FU/leucovorin (30 mg.cntdot.kg-1) had no effect on the kinetics and level of antibody response to Gastrimmune. Gastrimmune (200 .mu.g.cntdot.ml-1) and 5-FU/leucovorin combinations (12.5 and 20 mg.cntdot.kg-1) increased the therapeutic effects on the in vivo growth of DHDK12 tumors when compared to the agents given singly. Gastrimmune immunization may be a therapeutic option for the treatment of colorectal cancer in combination with 5-FU/leucovorin.

L25 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2002 ACS

1996:104643 Document No. 124:221116 Gastrimmune raises antibodies that neutralize amidated and glycine-extended **gastrin-17** and inhibit the growth of colon cancer. Watson, Susan A.; Michaeli, Dov; Grimes, Stephen; Morris, Teresa M.; Robinson, Graham; Varro, Andrea; Justin, Timothy A.; Hardcastle, Jack D. (Cancer Studies Unit, University of Nottingham, Nottingham, NG7 2UH, UK). Cancer Research, 56(4), 880-5 (English) 1996. CODEN: CNREA8. ISSN: 0008-5472. Publisher: American Association for Cancer Research.

AB The effect of gastrin neutralization was evaluated on the in vivo growth of the rat colon line, DHDK12, which expressed cholecystokinin B/gastrin receptors and secreted glycine-extended **gastrin-17** (G17). Gastrin neutralization was achieved by administration of the immunogen, Gastrimmune, which is composed of the amino terminal portion of G17 linked to a diphtheria toxoid. A rat-specific version of Gastrimmune was used to preimmunize rats, with control animals receiving diphtheria toxoid only. The antibodies raised neutralized both carboxy-amidated and glycine-extended G17. The tumor was implanted into the muscle layer of the abdominal wall, and rats immunized with Gastrimmune had significantly reduced median cross-sectional tumor areas (70.2% redn.) and wts. (56.5% redn.) when compared to control rats. Histol. anal. revealed that the tumors had an enhanced degree of necrosis with the area of viable tumor in the Gastrimmune-immunized rat reduced to 40.3% compared to 58.6% in the control rats. Immunization with Gastrimmune raised antibodies that inhibited the growth of a rat colon tumor. This could have been mediated by neutralization of both serum G17 and cell-assocd. precursor gastrin mols.

L25 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2002 ACS

1995:741182 Document No. 123:141724 Vaccines containing improved immunogenic peptide compositions against human **gastrin 17**. Gevas, Philip C.; Grimes, Stephen; Karr, Stephen L.; Michaeli, Dov; Scibienski, Robert (Aphton Corp., USA). PCT Int. Appl. WO 9513297 A2 19950518, 17 pp. DESIGNATED STATES: W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, NL, NO, NZ, PL, PT, RO, RU, SE, SI, SK, TJ, TT, UA, UZ, VN; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2.

APPLICATION: WO 1994-US13205 19941110. PRIORITY: US 1993-151219 19931112.

AB An improved immunogenic compn. against human **gastrin 17** (hG17) is presented which comprises the peptide pGlu-Gly-Pro-Trp-Leu-Glu-Glu-Glu-Glu-Ser-Ser-Pro-Pro-Pro-Pro-Cys (I) coupled to an immunogenic carrier and pharmaceutical compns. contg. the same. Thus, I coupled to diphtheria toxoid was used as an immunogen in rabbits. It induced a rapid and potent antibody response against hG17. On the 42nd day after the immunogen was injected, a mean antibody level of 227 pmole of hG17 bound per mL of antiserum had been induced in the rabbits. Specific anti-hG17 antibodies which neutralize the action of hG17 may be used to treat diseases in which hG17 is involved [no data].

L25 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2002 ACS

1992:509708 Document No. 117:109708 Induction and detection of anti-peptide antibody specificity is critically affected by the mode of hapten presentation. Moroder, Luis; Papini, Annamaria; Siglmueller, Gabriele; Koecher, Klaus; Doerrer, Elke; Schneider, Conrad H. (Max-Planck-Inst. Biochem., Martinsried, W-8033, Germany). Biological Chemistry Hoppe-Seyler, 373(6), 315-21 (English) 1992. CODEN: BCHSEI. ISSN: 0177-3593.

AB C-Terminal cholecystokinin (CCK)-peptides of increasing chain lengths were all linked at their N-termini to the single surface-exposed cysteine residue 107 of yeast iso-1-cytochrome c by the maleimide/thiol reaction. The resulting CCK/cytochrome 1:1 **conjugates** with the haptenic peptides in the identical protein environment were used to immunize outbred guinea pigs in order to assess the crit. size of CCK peptides required for the expression of a CCK-specific epitope and the induction of antibodies not cross-reacting with the homologous gastrin sequence. By using std. ELISA techniques with polystyrene-adsorbed antigen to evaluate the specificity of the antisera, none of the **conjugates** were found to induce anti-CCK antisera not cross-reacting with gastrin. However, when the biotinyl-CCK-antigen was immobilized by polystyrene-adsorbed avidin, i.e. via a procedure which assures max. accessibility of the bound antigen, CCK-12 and particularly CCK-13, linked through their N-termini to the carrier, exhibited the crit. length for the expression and recognition of a CCK-specific epitope. The related polyclonal antisera did not cross-react with the homologous gastrin in the modified ELISA.

L25 ANSWER 13 OF 17 MEDLINE

91210021 Document Number: 91210021. PubMed ID: 1708369. Fully synthetic immunogens. Part III. Synthesis of hinge-peptide/gastrin **conjugates** and their immunological properties. Wunsch E; Moroder L; Hubener G; Musiol H J; Von Grunigen R; Gohring W; Scharf R; Schneider C H. (Max Planck Institute of Biochemistry, Department of Peptide Chemistry, Martinsried, FRG.) INTERNATIONAL JOURNAL OF PEPTIDE AND PROTEIN RESEARCH, (1991 Feb) 37 (2) 90-102. Journal code: 0330420. ISSN: 0367-8377. Pub. country: Denmark. Language: English.

AB As core molecule for the multiple attachment of antigenic peptides we have selected the human IgG1 hinge fragment 225-232/225'-232'. Two types of **conjugates** of this double-chain bis-cystinyl hinge-peptide were prepared i) by linking its C-termini to [NIe15]-human-little-gastrin-[2,17] and ii) by elongating the resulting hinge-peptide/[NIe15]-little-gastrin-[2-17] **conjugate** at the two N-termini with the human big-gastrin sequence 1-14 to produce the big-gastrin-[1-14]/hinge-peptide/little-gastrin-[2-17] **conjugate**. For the synthesis of these peptide structures both the route via the preformed double-chain bis-cystinyl peptide and the route via suitably protected monomeric bis-cysteinyl peptides were used. For the latter approach advantage was taken of the previous observation about the preferred oxidation of the bis-cysteinyl hinge-peptide 225-232 to the dimer in parallel alignment. Both synthetic routes led to identical products. Immunization experiments in guinea pigs with the synthetic hybrids led to surprisingly strong

immune responses with anti-little-gastrin antibody titers comparable to those induced by the iso-1-cytochrome c/little-gastrin-[2-17] **conjugate** as carrier-hapten system. These findings show that the two gastrin constructs are fully competent immunogens. Additionally, the gastrin receptor-like specificity of the antibodies indicates that both the synthetic hybrids and the cytochrome c **conjugate** allow for expression of a little-gastrin-specific conformational epitope similar to the bioactive structure of this hormone. The usefulness of such synthetic hybrids is further confirmed by the observation that the bivalent immunogen, containing both the little-gastrin 2-17 and the big-gastrin 1-14 sequence, is capable of inducing an immune response against both antigenic sequences, although with different efficiency. These results fully confirm our expectations.

L25 ANSWER 14 OF 17 MEDLINE

90121757 Document Number: 90121757. PubMed ID: 2610937. Muramyl-peptide/gastrin **conjugates** as potential immunogens. Moroder L; Dufresne M; Gohring W; Wunsch E; Leidinger E; Gemeiner M. (Max-Planck-Institut fur Biochemie, Abteilung Peptidchemie, Martinsried bei Munchen.) BIOLOGICAL CHEMISTRY HOPPE-SEYLER, (1989 Nov) 370 (11) 1209-14. Journal code: 8503054. ISSN: 0177-3593. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB For a selective covalent linkage of muramyl-peptides with human-little-gastrin the maleimide-thiol reaction principle was adopted. For this purpose thiol-functionalized muramyl-peptide derivatives, i.e. N-acetyl-muramyl-alanyl-D-isoglutaminyl-cysteamine and N-acetyl-muramyl-alanyl-D-isoglutaminyl-N epsilon-palmitoyl-lysyl-cysteamine, were reacted with N alpha-maleoyl-beta-alanyl-[15-methoxinine]-human-little-g ast rin-I-[2-17]. The resulting gastrin **conjugates** were used in immunization experiments on rabbits and mice. Unexpectedly, these gastrin derivatives proved to be poorly immunogenic despite the built-in immunoadjuvanticity. The titers of the antipeptide antibodies as well as of the unspecific immunoglobulins were in the range of those of the control group.

L25 ANSWER 15 OF 17 MEDLINE

87299020 Document Number: 87299020. PubMed ID: 3304343. Studies on immunoassays of peptide factors. IV. New synthesis of a gastrin/peroxidase **conjugate**. Moroder L; Mourier G; Bovermann G; Dufresne M; Gohring W; Gemeiner M; Wunsch E. BIOLOGICAL CHEMISTRY HOPPE-SEYLER, (1987 Jul) 368 (7) 849-53. Journal code: 8503054. ISSN: 0177-3593. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB We have shown that structurally well-defined homogeneous maleoyl-peptides are synthetically accessible. These anchor-modified peptide derivatives allow their selective covalent linkage to thiol-containing proteins via the maleimide-thiol procedure. Correspondingly mercaptosuccinylated horseradish peroxidase was reacted with N alpha-maleoyl-beta-alanyl-human-little gastrin-I-[2-17] to produce the gastrin/peroxidase **conjugate** in good yields at 1:1 stoichiometry. The **conjugate** exhibited full enzymatic activity and identical binding affinity to antigastrin antisera as the parent gastrin. This approach proved to be well suited for the preparation of enzyme labeled peptide factors as tracers for immunoassays.

L25 ANSWER 16 OF 17 MEDLINE

87299019 Document Number: 87299019. PubMed ID: 3040037. Studies on immunoassays of peptide factors. III. Gastrin/iso-1-cytochrome C as immunogen for raising anti-gastrin antisera. Moroder L; Mourier G; Dufresne M; Bovermann G; Gohring W; Gemeiner M; Wunsch E. BIOLOGICAL CHEMISTRY HOPPE-SEYLER, (1987 Jul) 368 (7) 839-48. Journal code: 8503054. ISSN: 0177-3593. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB Iso-1-cytochrome c contains in penultimate position of its sequence a

cysteine residue which in analogy to the known tertiary structures of cytochromes c should be exposed on the surface of the protein. Its selective reaction with N alpha-maleoyl-beta-alanyl-human-little-gastrin-I-[2-17] led to a well characterized and homogeneous gastrin **conjugate** to be used as immunogen in rabbits. The antisera raised by this procedure exhibited a degree of specificity for the hormone gastrin parallel to that of the gastrin receptor. This is clearly documented by comparison of the immune crossreactivities of gastrin-peptides of increasing chain length and of fragments corresponding to various regions of the hormone molecule with their biological activity. The immune response provoked in the animals by the use of an homogeneous immunogen was found to be highly reproducible in terms of specificity of the antigastrin antibodies.

L25 ANSWER 17 OF 17 MEDLINE DUPLICATE 1
85216859 Document Number: 85216859. PubMed ID: 2408286. Effect of CCK antibodies on food intake and weight gain in Zucker rats. McLaughlin C L; Baile C A; Buonomo F C. PHYSIOLOGY AND BEHAVIOR, (1985 Feb) 34 (2) 277-82. Journal code: 0151504. ISSN: 0031-9384. Pub. country: United States. Language: English.

AB While exogenous administration of cholecystokinin (CCK) decreases food intake in many species, it has not been demonstrated conclusively that CCK is necessary for satiety to occur. In these experiments the role of CCK in eliciting satiety was further investigated by using endogenously produced and exogenously administered antibodies to CCK which were hypothesized to sequester circulating CCK. In the first experiment Zucker obese (n = 12, 192 +/- 16 g) and lean (n = 12, 152 +/- 11 g) male rats were administered CCK-8 conjugated to bovine serum albumin or bovine serum albumin by subcutaneous administration in Freund's adjuvant. Average percent binding of 125I-**gastrin-17** by serum taken 4, 8 and 12 weeks after treatment initiation was increased (19.9 vs. 2.1, p less than 0.001) in rats treated with CCK **conjugate** than controls, and the increase was greater in lean (27.5 vs. 1.9) than in obese (12.2 vs. 2.2, p less than 0.001) rats. In lean, but not obese rats, average daily food intake and weight gain were increased (9 and 17% p less than 0.04 and p less than 0.02 respectively) in rats with CCK-AB compared with rats with no CCK-AB during the three months. Development of CCK-AB did not affect food intake response to exogenously administered CCK-8 or pancreas weight relative to body weight. In Experiment 2 increased food intakes of obese and lean rats 30 min after intraperitoneal injection of rabbit serum with CCK-AB were greater than those after intraperitoneal injection of rabbit serum without CCK-AB (1.92 vs. 1.41, g, p less than 0.007).(ABSTRACT TRUNCATED AT 250 WORDS)

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L26 1468 (GRIMES S?/AU OR BLACKBURN P?/AU)

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L27 1 L26 AND SQUALENE

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L27 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
2001:472459 Document No. 135:66189 A stable immunogenic composition for frozen storage containing protein carriers. **Grimes, Stephen; Blackburn, Peter** (Aphton Corporation, USA). PCT Int. Appl. WO 2001045670 A2 20010628, 48 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF,

BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US35248 20001222. PRIORITY: US 1999-PV173022 19991223.

AB An injectable vaccine compn. comprising an immunogenic conjugate in an emulsion contg. advantageous oily vehicles is disclosed as suitable for frozen storage; moreover, a water-in-oil emulsion compn. is found to enhance immunogenicity after storage at about -18.degree.. For example, an aq. phase droplets of an anti-gastrin immunogenic emulsion (e.g., human gastrin 17(1-9)Ser 9-diphtheria toxoid conjugate) were stable at -70.degree., -18.degree., and 4.degree., but less stable at 25.degree.. The conjugate purity was most stable at -70.degree. and -18.degree., less stable at 4.degree. and much less stable at 25.degree.. The behavior in the release assay was not altered by storage at any four select temps. The immunogenicity response was unaffected by storage at 4.degree.. Storage at -18.degree. increased immunogenicity. The finding that it was possible to enhance immunogenicity by a single freeze-thaw cycle (freezing at -18.degree.) was unexpected. Although storage at -70.degree. and 25.degree. resulted in more variable responses, there was no clear trend that might be predictive for length of feasible storage time; in addn., immunogenicity was not altered from the time 0 control. However, not all emulsion formulations showed the stable storability according to this invention. Accordingly, the emulsions capable of withstanding freezing have been found to include Montanide ISA 25, 703, 719, and 720.

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L28 1 L26 AND SQUALANE

=> d l28 cbib abs

L28 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
2001:472459 Document No. 135:66189 A stable immunogenic composition for frozen storage containing protein carriers. **Grimes, Stephen; Blackburn, Peter** (Aphton Corporation, USA). PCT Int. Appl. WO 2001045670 A2 20010628, 48 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US35248 20001222. PRIORITY: US 1999-PV173022 19991223.

AB An injectable vaccine compn. comprising an immunogenic conjugate in an emulsion contg. advantageous oily vehicles is disclosed as suitable for frozen storage; moreover, a water-in-oil emulsion compn. is found to enhance immunogenicity after storage at about -18.degree.. For example, an aq. phase droplets of an anti-gastrin immunogenic emulsion (e.g., human gastrin 17(1-9)Ser 9-diphtheria toxoid conjugate) were stable at -70.degree., -18.degree., and 4.degree., but less stable at 25.degree.. The conjugate purity was most stable at -70.degree. and -18.degree., less stable at 4.degree. and much less stable at 25.degree.. The behavior in the release assay was not altered by storage at any four select temps. The immunogenicity response was unaffected by storage at 4.degree.. Storage at -18.degree. increased immunogenicity. The finding that it was possible to enhance immunogenicity by a single freeze-thaw cycle (freezing at -18.degree.) was unexpected. Although storage at -70.degree. and 25.degree. resulted in more variable responses, there was no clear trend that might be predictive for length of feasible storage time; in addn., immunogenicity was not altered from the time 0 control. However, not all emulsion formulations showed the stable storability according to this

invention. Accordingly, the emulsions capable of withstanding freezing have been found to include Montanide ISA 25, 703, 719, and 720.

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L30 ANSWER 1 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2002:368042 Document No.: PREV200200368042. Endocytosis of gastrin analogue peptides by tumour cell lines. Stubbs, M. (1); Khan, K. (1); **Grimes, S. (1)**; Michaeli, D. (1); Watson, S. A. (1); Caplin, M. E. (1). (1) Medical School, Royal Free and University College, Pond Street, London, NW3 2PF UK. Gut, (April, 2002) Vol. 50, No. Supplement 2, pp. A111. http://gut.bmjjournals.com/. print. Meeting Info.: Annual Meeting of the British Society of Gastroenterology Birmingham, England, UK March 17-20, 2002 British Society of Gastroenterology. ISSN: 0017-5749. Language: English.

L30 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2002 ACS
2001:472459 Document No. 135:66189 A stable immunogenic composition for frozen storage containing protein carriers. **Grimes, Stephen; Blackburn, Peter** (Aphton Corporation, USA). PCT Int. Appl. WO 2001045670 A2 20010628, 48 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US35248 20001222. PRIORITY: US 1999-PV173022 19991223.

AB An injectable vaccine compn. comprising an immunogenic conjugate in an emulsion contg. advantageous oily vehicles is disclosed as suitable for frozen storage; moreover, a water-in-oil emulsion compn. is found to enhance immunogenicity after storage at about -18.degree.. For example, an aq. phase droplets of an anti-gastrin immunogenic emulsion (e.g., human **gastrin 17**(1-9)Ser 9-diphtheria toxoid conjugate) were stable at -70.degree., -18.degree., and 4.degree., but less stable at 25.degree.. The conjugate purity was most stable at -70.degree. and -18.degree., less stable at 4.degree. and much less stable at 25.degree.. The behavior in the release assay was not altered by storage at any four select temps. The immunogenicity response was unaffected by storage at 4.degree.. Storage at -18.degree. increased immunogenicity. The finding that it was possible to enhance immunogenicity by a single freeze-thaw cycle (freezing at -18.degree.) was unexpected. Although storage at -70.degree. and 25.degree. resulted in more variable responses, there was no clear trend that might be predictive for length of feasible storage time; in addn., immunogenicity was not altered from the time 0 control. However, not all emulsion formulations showed the stable storability according to this invention. Accordingly, the emulsions capable of withstanding freezing have been found to include Montanide ISA 25, 703,

719, and 720.

L30 ANSWER 3 OF 17 MEDLINE DUPLICATE 1
2001431227 Document Number: 21370761. PubMed ID: 11478485. Effect of gastrin and anti-gastrin antibodies on proliferation of hepatocyte cell lines. Caplin M; Khan K; **Grimes S**; Michaeli D; Savage K; Pounder R; Dhillon A. (Department of Medicine, Royal Free Hospital School, London, UK.) DIGESTIVE DISEASES AND SCIENCES, (2001 Jul) 46 (7) 1356-66. Journal code: 7902782. ISSN: 0163-2116. Pub. country: United States. Language: English.

AB Gastrin (G-17) and its precursor glycine-extended gastrin (G-17-gly) have been shown to be trophic to some gastrointestinal tumors. This in vitro study assessed the effect of G-17, G-17-gly, anti-gastrin antibodies (anti-G-17), and the CCK-B receptor antagonist PD135,158 on three hepatoma cell lines (PLC/PRF/5, HepG2 and MCA-RH7777) and an embryonic liver cell line (WRL68). The pancreatic adenocarcinoma cell line AR42J was used as a positive control. G-17 and G-17-gly caused significant proliferation of AR42J and WRL68 cell lines. G-17-gly but not G-17 induced significant proliferation of the PLC/PRF/5 cell line. Anti-G-17 and PD135,158 significantly inhibited unstimulated AR42J and WRL68 cell lines. Anti-G-17 also inhibited the proliferative effects of G-17 and G-17-gly on AR42J, WRL68, and PLC/PRF/5 cell lines, whereas PD135,158 inhibited the proliferative effect of G-17 only. G-17 and G-17-gly as well as anti-G-17 and PD135,158 had no effect on HepG2 and MCA-RH77777 cell lines. It is concluded that G-17-stimulated proliferation is mediated via the CCK-B receptor and G-17-gly via a separate, as yet uncharacterized, receptor. There may therefore be a role for gastrin in embryonic hepatocellular proliferation and perhaps also in the proliferation of some hepatocellular tumors.

L30 ANSWER 4 OF 17 MEDLINE DUPLICATE 2
2001312445 Document Number: 21279537. PubMed ID: 11384777. Antibodies raised against the extracellular tail of the CCKB/gastrin receptor inhibit gastrin-stimulated signalling. McWilliams D F; **Grimes S**; Watson S A. (Academic Unit of Cancer Studies, D Floor West Block, QMC University Hospital, NG7 2UH, Nottingham, UK.. dan.mcwilliams@nottingham.ac.uk) . REGULATORY PEPTIDES, (2001 Jun 15) 99 (2-3) 157-61. Journal code: 8100479. ISSN: 0167-0115. Pub. country: Netherlands. Language: English.

AB INTRODUCTION: Gastrin acts to stimulate gastric acid secretion and is an acknowledged growth factor for human gastrointestinal (GI) cancer. The identity of the exact receptor type mediating the growth promoting effects of gastrin in tumours is uncertain. However, the best-characterised gastrin receptor is the CCK receptor type B (CCKB)/gastrin receptor. The anti-GRE1 antibody is a polyclonal, affinity-purified antibody raised against GRE1, a synthetic 21 amino acid peptide homologous to part of the extracellular, N-terminal tail of the CCKB receptor. We have recently proven that GRE1 antiserum specifically localises CCKB receptors on CCKB receptor transfected NIH3T3 cells and human gastrointestinal tumour cells by Western blotting and immunocytochemistry. GRE1 antiserum also inhibits liver invasion in the C170HM2 colorectal liver-metastasis model. AIM: To relate the ability of GRE1 antiserum to displace G17 from CCKB receptors with its impact on cellular transduction effects. METHODS: Radioligand binding studies were performed with 125IG17 and Calcium mobilisation studies by use of the fluorescent dye Fura 2-am. RESULTS: GRE1 antiserum competitively displaced 50% radiolabelled **gastrin-17** from whole cell NIH3T3 CCKB transfectants at a protein concentration of 250 microg x ml(-1). GRE1 antiserum did not stimulate calcium ion influx in the transfectant NIH3T3 cells when used at a range of protein concentrations. Pre-incubation with GRE1 antiserum was required to inhibit gastrin-stimulated calcium ion influx. This was found to be concentration-dependent, with inhibition shown at 30 and 5 microg x ml(-1) but not at 500 ng x ml(-1) or below. CONCLUSION: The GRE1 antiserum is specific for the CCKB receptor and may act to inhibit gastrin-stimulated

signalling in tumour cells.

L30 ANSWER 5 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2000:262166 Document No.: PREV200000262166. A study of the efficacy of gastrimmune in the adjuvant treatment of colorectal cancer. Henwood, Mark (1); Smith, Andrew M.; Watson, Susan A.; Justin, Tim; Michaeli, Dov; **Grimes, Steve**; Bush, Debbie; Scholefield, John H.; Hardcastle, Jack D.. (1) Section of Surg, Univ of Nottingham, Nottingham UK. Gastroenterology, (April, 2000) Vol. 118, No. 4 Suppl. 2 Part 1, pp. AGA A518-AGA A519. print.. Meeting Info.: 101st Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Diego, California, USA May 21-24, 2000 American Gastroenterological Association. ISSN: 0016-5085. Language: English. Summary Language: English.

L30 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2002 ACS
1999:753110 Document No. 131:350281 Immunological control of hypergastrinemia. Gevas, Philip C.; **Grimes, Stephen**; Karr, Stephen; Michaeli, Dov; Watson, Susan (Aphton Corporation, USA). PCT Int. Appl. WO 9959631 A1 19991125, 44 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US10751 19990514. PRIORITY: US 1998-85714 19980515.
AB Serum-assocd. hypergastrinemia is treated by administration of gastrin active or passive immunization. An anti-gastrin immunogenic compn. comprising a gastrin G17 or G34 peptide fragment which is amino acid spacer-linked to an immunogenic carrier, is administered to effectively neutralize the circulating gastrin hormone, and moreover, inhibit autocrine activity by progastrin such as Gly-extended G17, and amidated G17, in patients with pernicious anemia. Moreover, the method includes administration of a therapeutically effective amt. of anti-G17 or anti-G34 antibodies which may be in humanized form. Finally, the method provides ameliorating treatment of hypergastrinemic effects of proton pump inhibitors or H2 histamine receptor blocking agents or antagonists, in addn. to treatment of hypergastrinemia caused by diseases such as pernicious anemia.

L30 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2002 ACS
1999:753108 Document No. 132:439 Anti-heptadecagastrin immunogenic compn. immunization in combination with the administration of chemotherapeutic agents for the treatment of gastrin-dependent tumors. Gevas, Philip C.; **Grimes, Stephen**; Karr, Stephen L.; Watson, Susan A.; Michaeli, Dov (Aphton Corporation, USA). PCT Int. Appl. WO 9959628 A2 19991125, 25 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US10750 19990514. PRIORITY: US 1998-85687 19980515.
AB The invention relates to a combination therapy method for treating gastrin-dependent tumors. The method comprises the immunization of a patient with an anti-heptadecagastrin immunogenic compn. in combination with the administration of chemotherapeutic agents such as 5-fluorouracil and leucovorin.

L30 ANSWER 8 OF 17 CAPLUS COPYRIGHT 2002 ACS

1999:753096 Document No. 132:452 Method for the treatment of gastroesophageal reflux disease using anti-gastrin immunogenic compn. immunization combination with H2 antagonist or proton pump inhibitor. Gevas, Philip C.; **Grimes, Stephen**; Karr, Stephen; Michaeli, Dov (Aphton Corporation, USA). PCT Int. Appl. WO 9959612 A1 19991125, 24 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US10734 19990514. PRIORITY: US 1998-85610 19980515.

AB A method for the treatment of gastroesophageal reflux disease comprises a combination of active immunization with an anti-gastrin immunogenic compn. with an antagonist which blocks or inhibits the gastric acid pump activity; or alternatively administering purified anti-gastrin antibodies with a H2 antagonist or proton pump inhibitor of the gastric acid producing enzyme system.

L30 ANSWER 9 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

1999:320937 Document No.: PREV199900320937. The effect of antibodies raised against gastrimmune(R) on the proliferation of human pancreatic carcinoma cell lines. Brett, Bernard T. (1); Khan, Korsa (1); Savage, Kay (1); Michaeli, Dov; **Grimes, Steven**; Pounder, Roy E.; Dhillon, Amar P.; Caplin, Martyn E.. (1) Royal Free and Univ Coll Med Sch, London UK. Gastroenterology, (April, 1999) Vol. 116, No. 4 PART 2, pp. A382. Meeting Info.: Digestive Disease Week and the 100th Annual Meeting of the American Gastroenterological Association Orlando, Florida, USA May 16-19, 1999 American Gastroenterological Association. ISSN: 0016-5085. Language: English.

L30 ANSWER 10 OF 17 MEDLINE DUPLICATE 3

1998165357 Document Number: 98165357. PubMed ID: 9506532. Pre-clinical evaluation of the Gastrimmune immunogen alone and in combination with 5-fluorouracil/leucovorin in a rat colorectal cancer model. Watson S A; Michael D; Justin T A; **Grimes S**; Morris T M; Robinson G; Clarke P A; Hardcastle J D. (Department of Surgery, University Hospital, University of Nottingham, UK.. Sue.Watson@nottingham.ac.uk) . INTERNATIONAL JOURNAL OF CANCER, (1998 Mar 16) 75 (6) 873-7. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB Mature and post-translational precursor gastrin forms are growth factors for colorectal tumours. The immunogen Gastrimmune is composed of the amino terminus of **gastrin-17** linked to diphtheria toxoid and raises antibodies in situ which neutralise amidated and glycine-extended **gastrin-17**. The aim of the study was to determine the effect of treatment with 5-fluorouracil(5-FU)/leucovorin on the antibody titres induced by Gastrimmune and the effect of combination therapy on the growth of the rat colon tumour DHDK12. Gastrimmune was administered to rats s.c. at 3 weekly intervals. The rat colon tumour line DHDK12 was injected into the abdominal wall of BDIX rats. Combinations of 5-FU/leucovorin were injected i.v. on days 1, 3 and 5, with the cycle repeated every 4 weeks. Antibody titres were measured by an ELISA technique. Antibody titres were followed for 40 weeks after Gastrimmune (500 microg.ml(-1)) immunization, with titres peaking between 10 and 20 weeks after a single immunisation and falling by week 30. At termination, no effect was observed on either the histological appearance of the gastro-intestinal tract or the proliferation of the colonic mucosa. Pre- and post-treatment with 5-FU/leucovorin (30 mg.kg(-1)) had no effect on the kinetics and level of antibody response to Gastrimmune. Gastrimmune (200 microg.ml(-1)) and 5-FU/leucovorin combinations (12.5 and 20

mg.kg(-1)) increased the therapeutic effects on the in vivo growth of DHDK12 tumors when compared to the agents given singly. Gastrimmune immunisation may be a therapeutic option for the treatment of colorectal cancer in combination with 5-FU/leucovorin.

L30 ANSWER 11 OF 17 MEDLINE DUPLICATE 4
1998343355 Document Number: 98343355. PubMed ID: 9679761. Expression of CCKB/gastrin receptor isoforms in gastro-intestinal tumour cells. Watson S A; Clarke P A; Smith A M; Varro A; Michaeli D; **Grimes S**; Caplin M; Hardcastle J D. (Department of Surgery, University of Nottingham, UK.. sue.watson@nottingham.ac.uk) . INTERNATIONAL JOURNAL OF CANCER, (1998 Aug 12) 77 (4) 572-7. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB Anti-serum raised against the human cholecystokinin B (CCKB)/gastrin receptor was used in Western blotting to differentiate the cellular locations of receptor isoforms expressed by human gastro-intestinal (GI) tumour cell lines. Using anti-serum directed against the amino-terminal extracellular tail of the CCKB/gastrin receptor, 8/9 cell lines were shown to express immunoreactive proteins of either m.w. 70 or 40 kDa, or both. Both isoforms were found to be associated with intracellular, non-nuclear membranes, whereas only the 70 kDa protein was expressed in the plasma membrane. Receptor expression was related to gastrin production and secretion. Both progastrin and glycine-extended **gastrin-17** were produced and secreted by the tumour cell lines; however, carboxy amidated gastrin was not detected by radioimmunoassay. A CCKB/gastrin receptor transfectant NIH3T3 cell line did not produce detectable gastrin and showed exclusive expression of the 70 kDa receptor on the plasma membrane. One cell line had <50 pg/ml cell-associated progastrin and no detectable receptor form. Cell lines expressing 50-150 pg/ml had both 40 and 70 kDa receptor forms. Those expressing >150 pg/ml progastrin had only the 40 kDa isoform, which was shown to be exclusively expressed on intracellular, non-nuclear membranes, in one of the cell lines. Of the 4 cell lines exclusively expressing the lower m.w. receptor, 3 had gastrin present within the cell, which was not secreted. Thus, if cell-associated gastrin induces a proliferative effect, it may be by an intracrine pathway. Our study has identified the presence of CCKB/gastrin receptor isoforms in different cellular locations and may help toward understanding the complex autocrine and intracrine pathways mediated by gastrin peptides.

L30 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2002 ACS
1997:542351 Document No. 127:204461 Immunological methods for the treatment of gastrointestinal cancer. Gevas, Philip C.; Karr, Stephen L.; **Grimes, Stephen**; Michaeli, Dov; Watson, Susan A. (Aphton Corp., USA). PCT Int. Appl. WO 9728821 A1 19970814, 36 pp. DESIGNATED STATES: W: JP; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US2029 19970207. PRIORITY: US 1996-11411 19960208.

AB A method of treating gastrointestinal cancers dependent on the prohormones amidated **gastrin-17** and glycine-extended **gastrin-17**, comprising the administration to the patient of an anti-**gastrin-17** immunogen which induces antibodies which bind and neutralize amidated and glycine-extended **gastrin-17**. The gastrointestinal cancer is colorectal adenocarcinoma in mammal or human.

L30 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2002 ACS
1997:181660 Document No. 126:263155 Immunogenic compositions against gastrin peptides. Gevas, Philip C.; Karr, Stephen L.; **Grimes, Stephen**; Littenberg, Richard L. (Aphton Corp., USA). U.S. US 5607676 A 19970304, 25 pp., Cont.-in-part of U.S. Ser. No. 351,193, abandoned . (English). CODEN: USXXAM. APPLICATION: US 1991-721638 19910722. PRIORITY: US 1989-301353 19890124; US 1989-351193 19890512; WO 1990-US520 19900123.

AB Immunogenic compns. useful for the treatment of ulcers or tumors whose growth is dependent on or stimulated by gastrin hormones are disclosed. The immunogenic compns. induce antibodies in a subject which selectively neutralize the specific hormones. Pharmaceutical compns. comprising effective amts. of the immunogenic compns. and methods of treatment using the compns. are disclosed. A method of reversing the inventive treatments by neutralizing the antibodies induced in vivo is also disclosed.

L30 ANSWER 14 OF 17 MEDLINE DUPLICATE 5
96223701 Document Number: 96223701. PubMed ID: 8631028. Gastrimmune raises antibodies that neutralize amidated and glycine-extended **gastrin-17** and inhibit the growth of colon cancer.
Watson S A; Michaeli D; **Grimes S**; Morris T M; Robinson G; Varro A; Justin T A; Hardcastle J D. (Department of Surgery, Queen's Medical Centre, University of Nottingham, United Kingdom.) CANCER RESEARCH, (1996 Feb 15) 56 (4) 880-5. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB The effect of gastrin neutralization was evaluated on the in vivo growth of the rat colon line, DHDK12, which expressed cholecystokinin B/gastrin receptors and secreted glycine-extended **gastrin-17** (G17). Gastrin neutralization was achieved by administration of the immunogen, Gastrimmune, which is composed of the amino terminal portion of G17 linked to a diphtheria toxoid. A rat-specific version of Gastrimmune was used to preimmunize rats, with control animals receiving diphtheria toxoid only. The antibodies raised neutralized both carboxy-amidated and glycine-extended G17. The tumor was implanted into the muscle layer of the abdominal wall, and rats immunized with Gastrimmune had significantly reduced median cross-sectional tumor areas (70.2% reduction; P = 0.005) and weights (56.5% reduction; P = 0.0078)) when compared to control rats. Histological analysis revealed that the tumors had an enhanced degree of necrosis, with the area of viable tumor in the Gastrimmune-immunized rat reduced to 40.3% compared to 58.6% in the control rats (P = 0.003). Immunization with Gastrimmune raised antibodies that inhibited the growth of a rat colon tumor. This could have been mediated by neutralization of both serum G17 and cell-associated precursor gastrin molecules.

L30 ANSWER 15 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2002:32128 Document No.: PREV200200032128. Immunogenic compositions against human **gastrin 17**. Gevas, P. C.; **Grimes, S.**; Karr, S. L.; Michaeli, D.; Schbienski, R.. Honolulu, Hi USA. ASSIGNEE: APHTON CORP.. Patent Info.: US 5468494 Nov. 21, 1995. Official Gazette of the United States Patent and Trademark Office Patents, (Nov. 21, 1995) Vol. 1180, No. 3, pp. 1721. ISSN: 0098-1133. Language: English.

L30 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2002 ACS
1995:741182 Document No. 123:141724 Vaccines containing improved immunogenic peptide compositions against human **gastrin 17**. Gevas, Philip C.; **Grimes, Stephen**; Karr, Stephen L.; Michaeli, Dov; Scibienski, Robert (Aphton Corp., USA). PCT Int. Appl. WO 9513297 A2 19950518, 17 pp. DESIGNATED STATES: W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, NL, NO, NZ, PL, PT, RO, RU, SE, SI, SK, TJ, TT, UA, UZ, VN; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US13205 19941110. PRIORITY: US 1993-151219 19931112.

AB An improved immunogenic compn. against human **gastrin 17** (hG17) is presented which comprises the peptide pGlu-Gly-Pro-Trp-Leu-Glu-Glu-Glu-Glu-Ser-Ser-Pro-Pro-Pro-Pro-Cys (I) coupled to an immunogenic carrier and pharmaceutical compns. contg. the same. Thus, I coupled to diphtheria toxoid was used as an immunogen in rabbits. It induced a rapid and potent antibody response against hG17. On the 42nd day after the immunogen was injected, a mean antibody level of 227 pmole of hG17 bound

per mL of antiserum had been induced in the rabbits. Specific anti-hG17 antibodies which neutralize the action of hG17 may be used to treat diseases in which hG17 is involved [no data].

L30 ANSWER 17 OF 17 MEDLINE DUPLICATE 6
95221053 Document Number: 95221053. PubMed ID: 7705954. Anti-gastrin antibodies raised by gastrimmune inhibit growth of the human colorectal tumour AP5. Watson S A; Michaeli D; **Grimes S**; Morris T M; Crosbee D; Wilkinson M; Robinson G; Robertson J F; Steele R J; Hardcastle J D. (Department of Surgery, Queen's Medical Centre, Nottingham, UK.) INTERNATIONAL JOURNAL OF CANCER, (1995 Apr 10) 61 (2) 233-40. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB The neutralising ability of rabbit anti-**gastrin-17** (G17) antiserum raised by Gastrimmune, an immunogen constructed of the N-terminal portion of human G17 conjugated to diptheria toxoid (DT), was evaluated. The anti-serum (denoted anti-G17: DT) was shown to displace 125[I] G17 from the gastrin receptors on AR42J cells. The therapeutic effect of the rabbit anti-G17:DT anti-serum was evaluated on a freshly derived human colorectal cancer cell line, AP5, which was shown to express both gastrin receptors and gastrin immunoreactivity as assessed by immunocytochemistry. Rabbit anti-G17:DT anti-serum was shown to block basal in vitro growth of AP5 cells when used at an antigen binding capacity of 3.75 x 10(-9) M. The same dilution of anti-serum completely reversed growth stimulated by human G17 at concentrations of 1 x 10(-10) and 1 x 10(-9) M but did not inhibit growth at 1 x 10(-8) M G17. When AP5 was grown as a xenograft in nude mice, the sensitivity to the proliferative effect of human G17 was maintained. In addition, the basal growth of AP5 xenografts was significantly reduced by i.v. infusion of rabbit anti-G17:DT anti-serum when compared to treatment with rabbit anti:DT control anti-serum. Thus anti-G17:DT antibodies raised by Gastrimmune may be of clinical value in gastrin-sensitive tumours.

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